



Clinical trial results:

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo controlled, Phase IIb Efficacy and Safety Study of Adjunctive AZD6765 in Patients with Major Depressive Disorder (MDD) and a History of Inadequate Response to Antidepressants

Summary

EudraCT number	2011-004690-87
Trial protocol	SK
Global end of trial date	09 October 2013

Results information

Result version number	v1 (current)
This version publication date	27 May 2017
First version publication date	27 May 2017
Summary attachment (see zip file)	NS/D6702C00031-CSR Synopsis (D6702C00031_AZD6765_CSR_Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	D6702C00031
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Pepparedsleden 1, Mölndal, Sweden, SE-431 83
Public contact	Sanjeev Pathak, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Sanjeev Pathak, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 October 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 August 2013
Global end of trial reached?	Yes
Global end of trial date	09 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of AZD6765 (50 mg or 100 mg/infusion) as adjunct to current antidepressant medication versus antidepressant medication + placebo as assessed by the change from baseline to Week 6 in the MADRS total score in patients with MDD (DSM IV TR 296.2x or 296.3x) who exhibited an inadequate response to 3 or more different antidepressant treatments by history. Inadequate response was defined as persistent symptoms that, as judged by the investigator, continue to meet the diagnostic criteria for a Major Depressive Episode (MDE) according to the DSM IV TR.

Protection of trial subjects:

Treated in routine care.

Background therapy:

At least 1 antidepressant medication for a minimum of 6 weeks prior to randomization.

Evidence for comparator: -

Actual start date of recruitment	16 December 2011
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	Chile: 20
Country: Number of subjects enrolled	Slovakia: 27
Country: Number of subjects enrolled	South Africa: 17
Country: Number of subjects enrolled	United States: 238
Worldwide total number of subjects	302
EEA total number of subjects	27

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)	287
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multicenter study was conducted in Chile, Slovakia, South Africa, and the United States between 16 December 2011 and 26 August 2013. A total of 542 patients were enrolled in the study and of these, 302 patients were randomized to treatment. 240 patients were not randomized to treatment due to eligibility criteria not being fulfilled.

Pre-assignment

Screening details:

The study had a screening/washout period of up to 42 days, a 12-week double blind treatment period, and a 14-day follow-up period. Patients received 3 infusions per week during Weeks 1 to 3, 1 infusion per week during Weeks 4 to 6, and 1 infusion every other week during Weeks 7 to 12.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	AZD6765 50 mg

Arm description:

Intravenous infusion

Arm type	Experimental
Investigational medicinal product name	AZD6765
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Solution for Infusion, 0.5 mg/mL

Arm title	AZD6765 100 mg
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Arm description:

Intravenous infusion

Arm type	Experimental
Investigational medicinal product name	AZD6765
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Solution for Infusion, 1.0 mg/mL

Arm title	Placebo
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Arm description:

Intravenous infusion

Arm type	Placebo
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Solution for Infusion, 0.9% saline

Number of subjects in period 1	AZD6765 50 mg	AZD6765 100 mg	Placebo
Started	101	101	100
Completed	80	81	77
Not completed	21	20	23
Consent withdrawn by subject	10	7	12
Physician decision	-	1	-
Severe Non-Compliance to Protocol	1	-	1
Adverse event, non-fatal	1	7	3
Condition under Investigation Worsened	3	2	4
Lost to follow-up	3	2	1
Lack of efficacy	1	-	1
Study-Specific Withdrawal Criteria	2	-	1
Incorrect randomization	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	AZD6765 50 mg
Reporting group description:	
Intravenous infusion	
Reporting group title	AZD6765 100 mg
Reporting group description:	
Intravenous infusion	
Reporting group title	Placebo
Reporting group description:	
Intravenous infusion	

Reporting group values	AZD6765 50 mg	AZD6765 100 mg	Placebo
Number of subjects	101	101	100
Age categorical			
Units: Subjects			
Adults (18-39 years)	24	22	19
Adults (40-64 years)	74	74	74
65 years and over	3	5	7
Age Continuous			
Units: Years			
arithmetic mean	47.7	47.5	49.5
standard deviation	± 11.19	± 11.89	± 11.12
Gender, Male/Female			
Units: Subjects			
Female	62	70	65
Male	39	31	35
Race/Ethnicity, Customized			
Units: Subjects			
White	91	87	91
Black or African American	8	11	6
Asian	0	3	1
Other	2	0	2

Reporting group values	Total		
Number of subjects	302		
Age categorical			
Units: Subjects			
Adults (18-39 years)	65		
Adults (40-64 years)	222		
65 years and over	15		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		

Gender, Male/Female			
Units: Subjects			
Female	197		
Male	105		
Race/Ethnicity, Customized			
Units: Subjects			
White	269		
Black or African American	25		
Asian	4		
Other	4		

End points

End points reporting groups

Reporting group title	AZD6765 50 mg
Reporting group description: Intravenous infusion	
Reporting group title	AZD6765 100 mg
Reporting group description: Intravenous infusion	
Reporting group title	Placebo
Reporting group description: Intravenous infusion	

Primary: Change from baseline to Week 6 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score

End point title	Change from baseline to Week 6 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score
End point description: A 10-item scale for the evaluation of depressive symptoms. Each MADRS item is rated on a 0 to 6 scale. The MADRS total score is calculated as the sum of the 10 individual item scores; the total score can range from 0 to 60. Higher MADRS scores indicate higher levels of depressive symptoms.	
End point type	Primary
End point timeframe: Baseline to Week 6	

End point values	AZD6765 50 mg	AZD6765 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	100	97	
Units: units on a scale				
least squares mean (standard error)	-14.37 (\pm 1.238)	-14.4 (\pm 1.244)	-13.18 (\pm 1.266)	

Statistical analyses

Statistical analysis title	Change in MADRS total score - baseline to Week 6
Statistical analysis description: Mixed model repeated measures (MMRM) includes treatment, pooled center, visit, treatment by visit interaction, and baseline MADRS score by visit interaction as explanatory variables. Treatment, visit, treatment by visit interaction, and baseline MADRS score by visit interaction are fixed effects in the model; pooled center is a random effect.	
Comparison groups	Placebo v AZD6765 50 mg

Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.63 ^[1]
Method	Mixed models for repeated measures
Parameter estimate	LS mean difference
Point estimate	-1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.519
upper limit	2.152
Variability estimate	Standard error of the mean
Dispersion value	1.695

Notes:

[1] - The adjusted p-values protect the overall family-wise error rate across the 6 key comparisons of AZD6765 100 mg and 50 mg to placebo (for MADRS change from baseline to 6 weeks and to 12 weeks and for Sustained Response).

Statistical analysis title	Change in MADRS total score - baseline to Week 6
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Statistical analysis description:

MMRM includes treatment, pooled center, visit, treatment by visit interaction, and baseline MADRS score by visit interaction as explanatory variables. Treatment, visit, treatment by visit interaction, and baseline MADRS score by visit interaction are fixed effects in the model; pooled center is a random effect.

Comparison groups	AZD6765 100 mg v Placebo
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.476 ^[2]
Method	Mixed models for repeated measures
Parameter estimate	LS mean difference
Point estimate	-1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.563
upper limit	2.134
Variability estimate	Standard error of the mean
Dispersion value	1.701

Notes:

[2] - The adjusted p-values protect the overall family-wise error rate across the 6 key comparisons of AZD6765 100 mg and 50 mg to placebo (for MADRS change from baseline to 6 weeks and to 12 weeks and for Sustained Response).

Secondary: Change from baseline to Week 12 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score

End point title	Change from baseline to Week 12 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score
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End point description:

A 10-item scale for the evaluation of depressive symptoms. Each MADRS item is rated on a 0 to 6 scale. The MADRS total score is calculated as the sum of the 10 individual item scores; the total score can range from 0 to 60. Higher MADRS scores indicate higher levels of depressive symptoms.

End point type	Secondary
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End point timeframe:

Baseline to Week 12

End point values	AZD6765 50 mg	AZD6765 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	100	97	
Units: units on a scale				
least squares mean (standard error)	-15.97 (\pm 1.313)	-13.03 (\pm 1.332)	-13.92 (\pm 1.354)	

Statistical analyses

Statistical analysis title	Change in MADRS total score - baseline to Week 12
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Statistical analysis description:

Mixed model repeated measures (MMRM) includes treatment, pooled center, visit, treatment by visit interaction, and baseline MADRS score by visit interaction as explanatory variables. Treatment, visit, treatment by visit interaction, and baseline MADRS score by visit interaction are fixed effects in the model; pooled center is a random effect.

Comparison groups	AZD6765 50 mg v Placebo
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.63 ^[3]
Method	Mixed models for repeated measures
Parameter estimate	LS mean difference
Point estimate	-2.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.628
upper limit	1.522
Variability estimate	Standard error of the mean
Dispersion value	1.816

Notes:

[3] - The adjusted p-values protect the overall family-wise error rate across the 6 key comparisons of AZD6765 100 mg and 50 mg to placebo (for MADRS change from baseline to 6 weeks and to 12 weeks and for Sustained Response).

Statistical analysis title	Change in MADRS total score - baseline to Week 12
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Statistical analysis description:

MMRM includes treatment, pooled center, visit, treatment by visit interaction, and baseline MADRS score by visit interaction as explanatory variables. Treatment, visit, treatment by visit interaction, and baseline MADRS score by visit interaction are fixed effects in the model; pooled center is a random effect.

Comparison groups	AZD6765 100 mg v Placebo
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Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.63 ^[4]
Method	Mixed models for repeated measures
Parameter estimate	LS mean difference
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.72
upper limit	4.485
Variability estimate	Standard error of the mean
Dispersion value	1.83

Notes:

[4] - The adjusted p-values protect the overall family-wise error rate across the 6 key comparisons of AZD6765 100 mg and 50 mg to placebo (for MADRS change from baseline to 6 weeks and to 12 weeks and for Sustained Response).

Secondary: Percentage of patients with Sustained Response from Week 6 to Week 12 (defined as $\geq 50\%$ reduction from baseline in the MADRS total score at Week 6 and which is maintained through Week 12)

End point title	Percentage of patients with Sustained Response from Week 6 to Week 12 (defined as $\geq 50\%$ reduction from baseline in the MADRS total score at Week 6 and which is maintained through Week 12)
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End point description:

The percentage of patients with with Sustained Response (defined as $\geq 50\%$ reduction from baseline in the MADRS total score at Week 6 and which is maintained through Week 12) was calculated.

End point type	Secondary
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End point timeframe:

Week 6 to Week 12

End point values	AZD6765 50 mg	AZD6765 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	100	97	
Units: percentage of participants analyzed				
number (not applicable)	22.8	23	21.6	

Statistical analyses

Statistical analysis title	Sustained MADRS Response - Week 6 to Week 12
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Statistical analysis description:

Logistic regression model including treatment as a fixed effect and the baseline MADRS total score as a covariate.

Comparison groups	AZD6765 50 mg v Placebo
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Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.852 ^[5]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.544
upper limit	2.089
Variability estimate	Standard error of the mean
Dispersion value	0.366

Notes:

[5] - The adjusted p-values protect the overall family-wise error rate across the 6 key comparisons of AZD6765 100 mg and 50 mg to placebo (for MADRS change from baseline to 6 weeks and to 12 weeks and for Sustained Response).

Statistical analysis title	Sustained MADRS Response - Week 6 to Week 12
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Statistical analysis description:

Logistic regression model including treatment as a fixed effect and the baseline MADRS total score as a covariate.

Comparison groups	AZD6765 100 mg v Placebo
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.821 ^[6]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.552
upper limit	2.115
Variability estimate	Standard error of the mean
Dispersion value	0.37

Notes:

[6] - The adjusted p-values protect the overall family-wise error rate across the 6 key comparisons of AZD6765 100 mg and 50 mg to placebo (for MADRS change from baseline to 6 weeks and to 12 weeks and for Sustained Response).

Secondary: Percentage of patients who were Responders (defined as a $\geq 50\%$ reduction from baseline in MADRS total score) at Week 6

End point title	Percentage of patients who were Responders (defined as a $\geq 50\%$ reduction from baseline in MADRS total score) at Week 6
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End point description:

The percentage of patients who were Responders (defined as $\geq 50\%$ reduction from baseline in MADRS total score) was calculated.

End point type	Secondary
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End point timeframe:

Baseline to Week 6

End point values	AZD6765 50 mg	AZD6765 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	86	84	82	
Units: percentage of participants analyzed				
number (not applicable)	36	44	39	

Statistical analyses

Statistical analysis title	Adjusted odds ratio of Response at Week 6
Statistical analysis description:	
Generalized linear model of the repeated measures (GEE) with logic link including treatment, visit, and treatment by visit interaction as fixed effects and the baseline MADRS total score as a covariate.	
Comparison groups	AZD6765 50 mg v Placebo
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.751
Method	GEE for repeated measures
Parameter estimate	Odds ratio (OR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.485
upper limit	1.686
Variability estimate	Standard error of the mean
Dispersion value	0.318

Statistical analysis title	Adjusted odds ratio of Response at Week 6
Statistical analysis description:	
Generalized linear model of the repeated measures (GEE) with logic link including treatment, visit, and treatment by visit interaction as fixed effects and the baseline MADRS total score as a covariate.	
Comparison groups	AZD6765 100 mg v Placebo
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.555
Method	GEE for repeated measures
Parameter estimate	Odds ratio (OR)
Point estimate	1.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	2.233
Variability estimate	Standard error of the mean
Dispersion value	0.315

Secondary: Percentage of patients who were Responders (defined as a $\geq 50\%$ reduction from baseline in MADRS total score) at Week 12

End point title	Percentage of patients who were Responders (defined as a $\geq 50\%$ reduction from baseline in MADRS total score) at Week 12
End point description: The percentage of patients who were Responders (defined as $\geq 50\%$ reduction from baseline in MADRS total score) was calculated.	
End point type	Secondary
End point timeframe: Baseline to Week 12	

End point values	AZD6765 50 mg	AZD6765 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	85	81	
Units: percentage of participants analyzed				
number (not applicable)	48.3	36.5	40.7	

Statistical analyses

Statistical analysis title	Adjusted odds ratio of Response at Week 12
Statistical analysis description: Generalized linear model of the repeated measures (GEE) with logic link including treatment, visit, and treatment by visit interaction as fixed effects and the baseline MADRS total score as a covariate.	
Comparison groups	AZD6765 50 mg v Placebo
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.434
Method	GEE for repeated measures
Parameter estimate	Odds ratio (OR)
Point estimate	1.27

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.699
upper limit	2.301
Variability estimate	Standard error of the mean
Dispersion value	0.304

Statistical analysis title	Adjusted odds ratio of Response at Week 12
Statistical analysis description:	
Generalized linear model of the repeated measures (GEE) with logic link including treatment, visit, and treatment by visit interaction as fixed effects and the baseline MADRS total score as a covariate.	
Comparison groups	AZD6765 100 mg v Placebo
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.286
Method	GEE for repeated measures
Parameter estimate	Odds ratio (OR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.377
upper limit	1.334
Variability estimate	Standard error of the mean
Dispersion value	0.322

Secondary: Percentage of patients who were Remitted (defined as MADRS total score ≤10) at Week 6

End point title	Percentage of patients who were Remitted (defined as MADRS total score ≤10) at Week 6
End point description:	
The percentage of patients who were Remitted (defined as MADRS total score ≤10) was calculated.	
End point type	Secondary
End point timeframe:	
Baseline to Week 6	

End point values	AZD6765 50 mg	AZD6765 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	86	84	82	
Units: percentage of participants analyzed				
number (not applicable)	23.3	23.8	18.3	

Statistical analyses

Statistical analysis title	Adjusted odds ratio of Remission at Week 6
Statistical analysis description:	
Generalized linear model of the repeated measures (GEE) with logic link including treatment, visit, and treatment by visit interaction as fixed effects and the baseline MADRS total score as a covariate.	
Comparison groups	AZD6765 50 mg v Placebo
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.357
Method	GEE for repeated measures
Parameter estimate	Odds ratio (OR)
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.672
upper limit	3.007
Variability estimate	Standard error of the mean
Dispersion value	0.382

Statistical analysis title	Adjusted odds ratio of Remission at Week 6
Statistical analysis description:	
Generalized linear model of the repeated measures (GEE) with logic link including treatment, visit, and treatment by visit interaction as fixed effects and the baseline MADRS total score as a covariate.	
Comparison groups	AZD6765 100 mg v Placebo
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.463
Method	GEE for repeated measures
Parameter estimate	Odds ratio (OR)
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.622
upper limit	2.84
Variability estimate	Standard error of the mean
Dispersion value	0.387

Secondary: Percentage of patients who were Remitted (defined as MADRS total score ≤10) at Week 12

End point title	Percentage of patients who were Remitted (defined as MADRS total score ≤10) at Week 12
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End point description:

The percentage of patients who were Remitted (defined as MADRS total score ≤10) was calculated.

End point type	Secondary
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End point timeframe:

Baseline to Week 12

End point values	AZD6765 50 mg	AZD6765 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	85	81	
Units: percentage of participants analyzed				
number (not applicable)	27	22.4	25.9	

Statistical analyses

Statistical analysis title	Adjusted odds ratio of Remission at Week 12
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Statistical analysis description:

Generalized linear model of the repeated measures (GEE) with logic link including treatment, visit, and treatment by visit interaction as fixed effects and the baseline MADRS total score as a covariate.

Comparison groups	AZD6765 50 mg v Placebo
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.911
Method	GEE for repeated measures
Parameter estimate	Odds ratio (OR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.532
upper limit	2.031
Variability estimate	Standard error of the mean
Dispersion value	0.342

Statistical analysis title	Adjusted odds ratio of Remission at Week 12
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Statistical analysis description:

Generalized linear model of the repeated measures (GEE) with logic link including treatment, visit, and treatment by visit interaction as fixed effects and the baseline MADRS total score as a covariate.

Comparison groups	AZD6765 100 mg v Placebo
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.509
Method	GEE for repeated measures
Parameter estimate	Odds ratio (OR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.382
upper limit	1.613
Variability estimate	Standard error of the mean
Dispersion value	0.368

Secondary: Change from baseline in functional impairment as measured by the change from baseline in the Sheehan Disability Scale (SDS) total score

End point title	Change from baseline in functional impairment as measured by the change from baseline in the Sheehan Disability Scale (SDS) total score
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End point description:

A 3-item, self-administered scale that measures the extent a patient is impaired by their disease. Higher scores indicate more severe impairment. The SDS total score is calculated as the sum of the score for the 3 intercorrelated domains (school/work, social life, and family life/home responsibilities), ranges from 0 (no impairment) to 30 (most severe impairment).

End point type	Secondary
End point timeframe:	
Baseline to Week 12	

End point values	AZD6765 50 mg	AZD6765 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	100	97	
Units: units on a scale				
least squares mean (standard error)				
Week 6	-7.08 (± 0.959)	-6.9 (± 0.981)	-6.91 (± 0.989)	
Week 12	-6.98 (± 0.995)	-6.8 (± 1.021)	-8.09 (± 1.034)	

Statistical analyses

Statistical analysis title	Change in SDS total score - baseline to Week 6
Statistical analysis description:	
MMRM includes treatment, pooled center, visit, treatment by visit interaction, and baseline SDS score by visit interaction as explanatory variables. Treatment, visit, treatment by visit interaction, and baseline SDS score by visit interaction are fixed effects in the model; pooled center is a random effect.	
Comparison groups	AZD6765 50 mg v Placebo
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.889 ^[7]
Method	Mixed models for repeated measures
Parameter estimate	LS mean difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.609
upper limit	2.264
Variability estimate	Standard error of the mean
Dispersion value	1.238

Notes:

[7] - Analysis for change in SDS total score from baseline to Week 6

Statistical analysis title	Change in SDS total score - baseline to Week 6
Statistical analysis description:	
MMRM includes treatment, pooled center, visit, treatment by visit interaction, and baseline SDS score by visit interaction as explanatory variables. Treatment, visit, treatment by visit interaction, and baseline SDS score by visit interaction are fixed effects in the model; pooled center is a random effect.	
Comparison groups	AZD6765 100 mg v Placebo
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.992 ^[8]
Method	Mixed models for repeated measures
Parameter estimate	LS mean difference
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.477
upper limit	2.501
Variability estimate	Standard error of the mean
Dispersion value	1.264

Notes:

[8] - Analysis for change in SDS total score from baseline to Week 6

Statistical analysis title	Change in SDS total score - baseline to Week 12
Statistical analysis description:	
MMRM includes treatment, pooled center, visit, treatment by visit interaction, and baseline SDS score by visit interaction as explanatory variables. Treatment, visit, treatment by visit interaction, and baseline SDS score by visit interaction are fixed effects in the model; pooled center is a random effect.	
Comparison groups	AZD6765 50 mg v Placebo

Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.392 ^[9]
Method	Mixed models for repeated measures
Parameter estimate	LS mean difference
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.448
upper limit	3.678
Variability estimate	Standard error of the mean
Dispersion value	1.301

Notes:

[9] - Analysis for change in SDS total score from baseline to Week 12

Statistical analysis title	Change in SDS total score - baseline to Week 12
Statistical analysis description:	
MMRM includes treatment, pooled center, visit, treatment by visit interaction, and baseline SDS score by visit interaction as explanatory variables. Treatment, visit, treatment by visit interaction, and baseline SDS score by visit interaction are fixed effects in the model; pooled center is a random effect.	
Comparison groups	AZD6765 100 mg v Placebo
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.333 ^[10]
Method	Mixed models for repeated measures
Parameter estimate	LS mean difference
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.327
upper limit	3.908
Variability estimate	Standard error of the mean
Dispersion value	1.329

Notes:

[10] - Analysis for changed in SDS total score from baseline to Week 12

Secondary: Change in severity of depressive symptoms as measured by change from baseline in the Clinical Global Impression-Severity (CGI-S) score

End point title	Change in severity of depressive symptoms as measured by change from baseline in the Clinical Global Impression-Severity (CGI-S) score
End point description:	
Clinical Global Impression - Severity (CGI-S) scale rates the severity of the patient's illness at the time of assessment, range from 1 (normal, not ill) to 7 (very severely ill).	
End point type	Secondary
End point timeframe:	
Baseline to Week 12	

End point values	AZD6765 50 mg	AZD6765 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	100	97	
Units: units on a scale				
least squares mean (standard error)				
Week 6	-1.5 (± 0.16)	-1.5 (± 0.16)	-1.4 (± 0.16)	
Week 12	-1.8 (± 0.16)	-1.5 (± 0.16)	-1.6 (± 0.16)	

Statistical analyses

Statistical analysis title	Change in CGI-S score - baseline to Week 6
Statistical analysis description:	
MMRM includes treatment, pooled center, visit, treatment by visit interaction, and baseline CGI-S score by visit interaction as explanatory variables. Treatment, visit, treatment by visit interaction, and baseline CGI-S score by visit interaction are fixed effects in the model; pooled center is a random effect.	
Comparison groups	AZD6765 50 mg v Placebo
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.728 ^[11]
Method	Mixed models for repeated measures
Parameter estimate	LS mean difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	0.34
Variability estimate	Standard error of the mean
Dispersion value	0.21

Notes:

[11] - Analysis for change in CGI-S total score from baseline to Week 6

Statistical analysis title	Change in CGI-S score - baseline to Week 6
Statistical analysis description:	
MMRM includes treatment, pooled center, visit, treatment by visit interaction, and baseline CGI-S score by visit interaction as explanatory variables. Treatment, visit, treatment by visit interaction, and baseline CGI-S score by visit interaction are fixed effects in the model; pooled center is a random effect.	
Comparison groups	AZD6765 100 mg v Placebo

Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.562 ^[12]
Method	Mixed models for repeated measures
Parameter estimate	LS mean difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	0.29
Variability estimate	Standard error of the mean
Dispersion value	0.21

Notes:

[12] - Analysis for change in CGI-S total score from baseline to Week 6

Statistical analysis title	Change in CGI-S score - baseline to Week 12
Statistical analysis description:	
MMRM includes treatment, pooled center, visit, treatment by visit interaction, and baseline CGI-S score by visit interaction as explanatory variables. Treatment, visit, treatment by visit interaction, and baseline CGI-S score by visit interaction are fixed effects in the model; pooled center is a random effect.	
Comparison groups	AZD6765 50 mg v Placebo
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.283 ^[13]
Method	Mixed models for repeated measures
Parameter estimate	LS mean difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.64
upper limit	0.19
Variability estimate	Standard error of the mean
Dispersion value	0.21

Notes:

[13] - Analysis for change in CGI-S total score from baseline to Week 12

Statistical analysis title	Change in CGI-S score - baseline to Week 12
Statistical analysis description:	
MMRM includes treatment, pooled center, visit, treatment by visit interaction, and baseline CGI-S score by visit interaction as explanatory variables. Treatment, visit, treatment by visit interaction, and baseline CGI-S score by visit interaction are fixed effects in the model; pooled center is a random effect.	
Comparison groups	AZD6765 100 mg v Placebo

Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.54 ^[14]
Method	Mixed models for repeated measures
Parameter estimate	LS mean difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.55
Variability estimate	Standard error of the mean
Dispersion value	0.21

Notes:

[14] - Analysis for changed in CGI-S total score from baseline to Week 12

Secondary: Change in severity of depressive symptoms as measured by the CGI-I response (defined as CGI-I rating of “very much improved” or “much improved”) at Week 6

End point title	Change in severity of depressive symptoms as measured by the CGI-I response (defined as CGI-I rating of “very much improved” or “much improved”) at Week 6
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End point description:

A 3-part, clinician-administered scale that rates the improvement or worsening of the patient's illness from randomization (baseline). Each item is scored on a 1 to 7 scale. CGI-I scores >4 indicate worsening, while scores <4 indicate improvement.

End point type	Secondary
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End point timeframe:

Baseline to Week 6

End point values	AZD6765 50 mg	AZD6765 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	86	84	82	
Units: percentage of participants analyzed				
number (not applicable)	51.2	47.6	37.8	

Statistical analyses

Statistical analysis title	Response in CGI-I - baseline to Week 6
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Statistical analysis description:

Generalized linear model of the repeated measures (GEE) with logic link including treatment, visit, and treatment by visit interaction as fixed effects and the baseline CGI-S total score as a covariate.

Comparison groups	AZD6765 50 mg v Placebo
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Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.067
Method	GEE for repeated measures
Parameter estimate	Odds ratio (OR)
Point estimate	1.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.962
upper limit	3.141
Variability estimate	Standard error of the mean
Dispersion value	0.302

Statistical analysis title	Response in CGI-I - baseline to Week 6
Statistical analysis description:	
Generalized linear model of the repeated measures (GEE) with logic link including treatment, visit, and treatment by visit interaction as fixed effects and the baseline CGI-S total score as a covariate.	
Comparison groups	AZD6765 100 mg v Placebo
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.23
Method	GEE for repeated measures
Parameter estimate	Odds ratio (OR)
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.798
upper limit	2.558
Variability estimate	Standard error of the mean
Dispersion value	0.297

Secondary: Change in severity of depressive symptoms as measured by the CGI-I response (defined as CGI-I rating of “very much improved” or “much improved”) at Week 12

End point title	Change in severity of depressive symptoms as measured by the CGI-I response (defined as CGI-I rating of “very much improved” or “much improved”) at Week 12
End point description:	
A 3-part, clinician-administered scale that rates the improvement or worsening of the patient's illness from randomization (baseline). Each item is scored on a 1 to 7 scale. CGI-I scores >4 indicate worsening, while scores <4 indicate improvement.	
End point type	Secondary
End point timeframe:	
Baseline to Week 12	

End point values	AZD6765 50 mg	AZD6765 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	85	81	
Units: percentage of participants analyzed				
number (not applicable)	50.6	44.7	40.7	

Statistical analyses

Statistical analysis title	Response in CGI-I - baseline to Week 12
Statistical analysis description:	
Generalized linear model of the repeated measures (GEE) with logic link including treatment, visit, and treatment by visit interaction as fixed effects and the baseline CGI-S total score as a covariate.	
Comparison groups	AZD6765 50 mg v Placebo
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.268
Method	GEE for repeated measures
Parameter estimate	Odds ratio (OR)
Point estimate	1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	2.447
Variability estimate	Standard error of the mean
Dispersion value	0.292

Statistical analysis title	Response in CGI-I - baseline to Week 12
Statistical analysis description:	
Generalized linear model of the repeated measures (GEE) with logic link including treatment, visit, and treatment by visit interaction as fixed effects and the baseline CGI-S total score as a covariate.	
Comparison groups	AZD6765 100 mg v Placebo
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.909
Method	GEE for repeated measures
Parameter estimate	Odds ratio (OR)
Point estimate	0.97

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.533
upper limit	1.75
Variability estimate	Standard error of the mean
Dispersion value	0.303

Secondary: Change from baseline in self-rated severity of depressive symptoms as measured by Quick Inventory of Depressive Symptomatology Self-Rated 16-item scale (QIDS-SR-16) total score

End point title	Change from baseline in self-rated severity of depressive symptoms as measured by Quick Inventory of Depressive Symptomatology Self-Rated 16-item scale (QIDS-SR-16) total score
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End point description:

A 16-question self-report inventory that includes the 9 Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria symptom domains: sad mood, concentration, self-outlook, suicidal ideation, involvement, energy/fatigability, sleep disturbance (4 items: initial, middle, late insomnia, and hypersomnia), appetite/weight increased or decrease (4 items), and psychomotor agitation/retardation (2 items). The QIDS-SR-16 total scores range from 0 (least severe) to 27 (most severe).

End point type	Secondary
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End point timeframe:

Baseline to Week 12

End point values	AZD6765 50 mg	AZD6765 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	100	97	
Units: units on a scale				
least squares mean (standard error)				
Week 6	-8.7 (± 0.69)	-7.9 (± 0.7)	-8.1 (± 0.71)	
Week 12	-9.2 (± 0.7)	-7.6 (± 0.71)	-8.9 (± 0.72)	

Statistical analyses

Statistical analysis title	Change in QIDS-SR-16 score - baseline to Week 6
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Statistical analysis description:

MMRM includes treatment, pooled center, visit, treatment by visit interaction, and baseline QIDS-SR-16 total score by visit interaction as explanatory variables. Treatment, visit, treatment by visit interaction, and baseline QIDS-SR-16 total score by visit interaction are fixed effects in the model; pooled center is a random effect.

Comparison groups	AZD6765 50 mg v Placebo
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Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.505 ^[15]
Method	Mixed models for repeated measures
Parameter estimate	LS mean difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.29
upper limit	1.13
Variability estimate	Standard error of the mean
Dispersion value	0.87

Notes:

[15] - Analysis for change in QIDS-SR-16 total score from baseline to Week 6

Statistical analysis title	Change in QIDS-SR-16 score - baseline to Week 6
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Statistical analysis description:

MMRM includes treatment, pooled center, visit, treatment by visit interaction, and baseline QIDS-SR-16 total score by visit interaction as explanatory variables. Treatment, visit, treatment by visit interaction, and baseline QIDS-SR-16 total score by visit interaction are fixed effects in the model; pooled center is a random effect.

Comparison groups	AZD6765 100 mg v Placebo
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.842 ^[16]
Method	Mixed models for repeated measures
Parameter estimate	LS mean difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.56
upper limit	1.91
Variability estimate	Standard error of the mean
Dispersion value	0.88

Notes:

[16] - Analysis for change in QIDS-SR-16 total score from baseline to Week 6

Statistical analysis title	Change in QIDS-SR-16 score - baseline to Week 12
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Statistical analysis description:

MMRM includes treatment, pooled center, visit, treatment by visit interaction, and baseline QIDS-SR-16 total score by visit interaction as explanatory variables. Treatment, visit, treatment by visit interaction, and baseline QIDS-SR-16 total score by visit interaction are fixed effects in the model; pooled center is a random effect.

Comparison groups	AZD6765 50 mg v Placebo
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Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.788 ^[17]
Method	Mixed models for repeated measures
Parameter estimate	LS mean difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.98
upper limit	1.51
Variability estimate	Standard error of the mean
Dispersion value	0.89

Notes:

[17] - Analysis for change in QIDS-SR-16 total score from baseline to Week 12

Statistical analysis title	Change in QIDS-SR-16 score - baseline to Week 12
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Statistical analysis description:

MMRM includes treatment, pooled center, visit, treatment by visit interaction, and baseline QIDS-SR-16 total score by visit interaction as explanatory variables. Treatment, visit, treatment by visit interaction, and baseline QIDS-SR-16 total score by visit interaction are fixed effects in the model; pooled center is a random effect.

Comparison groups	AZD6765 100 mg v Placebo
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.133 ^[18]
Method	Mixed models for repeated measures
Parameter estimate	LS mean difference
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	3.12
Variability estimate	Standard error of the mean
Dispersion value	0.9

Notes:

[18] - Analysis for changed in QIDS-SR-16 total score from baseline to Week 12

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the time of signature of informed consent throughout the treatment period and follow-up period.

Adverse event reporting additional description:

The AZD6765iv (intravenous) 100 mg group had one less subject than the numbers provided in the Participant Flow Module because one subject who was randomized did not receive any study medication and thus was excluded from the efficacy and safety analysis sets.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	AZD6765iv 100 mg
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Reporting group description:

Intravenous infusion

Reporting group title	AZD6765iv 50 mg
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Reporting group description:

Intravenous infusion

Reporting group title	Placebo
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Reporting group description:

Intravenous infusion

Serious adverse events	AZD6765iv 100 mg	AZD6765iv 50 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 100 (4.00%)	2 / 101 (1.98%)	4 / 100 (4.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
ALCOHOL POISONING			
subjects affected / exposed	0 / 100 (0.00%)	0 / 101 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 100 (0.00%)	1 / 101 (0.99%)	0 / 100 (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			

NON-CARDIAC CHEST PAIN			
subjects affected / exposed	0 / 100 (0.00%)	0 / 101 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ASTHMA			
subjects affected / exposed	0 / 100 (0.00%)	1 / 101 (0.99%)	0 / 100 (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
Psychiatric disorders			
DEPRESSIVE SYMPTOM			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	0 / 100 (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
INTENTIONAL DRUG MISUSE			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	0 / 100 (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
MAJOR DEPRESSION			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	0 / 100 (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
SUICIDAL IDEATION			
subjects affected / exposed	0 / 100 (0.00%)	0 / 101 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUICIDE ATTEMPT			
subjects affected / exposed	0 / 100 (0.00%)	0 / 101 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
HEPATITIS C			

subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	0 / 100 (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

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

Non-serious adverse events	AZD6765iv 100 mg	AZD6765iv 50 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 100 (68.00%)	59 / 101 (58.42%)	47 / 100 (47.00%)
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	45 / 100 (45.00%)	27 / 101 (26.73%)	10 / 100 (10.00%)
occurrences (all)	205	63	17
HEADACHE			
subjects affected / exposed	17 / 100 (17.00%)	20 / 101 (19.80%)	18 / 100 (18.00%)
occurrences (all)	29	28	28
SEDATION			
subjects affected / exposed	7 / 100 (7.00%)	5 / 101 (4.95%)	5 / 100 (5.00%)
occurrences (all)	26	18	13
SOMNOLENCE			
subjects affected / exposed	6 / 100 (6.00%)	9 / 101 (8.91%)	7 / 100 (7.00%)
occurrences (all)	12	16	9
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	6 / 100 (6.00%)	5 / 101 (4.95%)	5 / 100 (5.00%)
occurrences (all)	6	6	6
FEELING DRUNK			
subjects affected / exposed	6 / 100 (6.00%)	1 / 101 (0.99%)	0 / 100 (0.00%)
occurrences (all)	38	1	0
Gastrointestinal disorders			
CONSTIPATION			
subjects affected / exposed	6 / 100 (6.00%)	2 / 101 (1.98%)	5 / 100 (5.00%)
occurrences (all)	6	2	5
DIARRHOEA			
subjects affected / exposed	5 / 100 (5.00%)	7 / 101 (6.93%)	5 / 100 (5.00%)
occurrences (all)	7	10	6

<p>DRY MOUTH</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>6 / 100 (6.00%)</p> <p>17</p>	<p>3 / 101 (2.97%)</p> <p>5</p>	<p>2 / 100 (2.00%)</p> <p>3</p>
<p>NAUSEA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>21 / 100 (21.00%)</p> <p>26</p>	<p>13 / 101 (12.87%)</p> <p>13</p>	<p>13 / 100 (13.00%)</p> <p>16</p>
<p>Psychiatric disorders</p> <p>DISSOCIATION</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>INSOMNIA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>8 / 100 (8.00%)</p> <p>37</p> <p>6 / 100 (6.00%)</p> <p>6</p>	<p>4 / 101 (3.96%)</p> <p>6</p> <p>5 / 101 (4.95%)</p> <p>6</p>	<p>4 / 100 (4.00%)</p> <p>7</p> <p>4 / 100 (4.00%)</p> <p>4</p>
<p>Musculoskeletal and connective tissue disorders</p> <p>BACK PAIN</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 100 (1.00%)</p> <p>1</p>	<p>7 / 101 (6.93%)</p> <p>9</p>	<p>2 / 100 (2.00%)</p> <p>2</p>
<p>Infections and infestations</p> <p>UPPER RESPIRATORY TRACT INFECTION</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>6 / 100 (6.00%)</p> <p>7</p>	<p>7 / 101 (6.93%)</p> <p>8</p>	<p>4 / 100 (4.00%)</p> <p>4</p>

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 February 2012	Clarifications regarding timing of assessments, strengthening of requirements for contraception to also include male patients and male partners, addition of a new exclusion criterion for patients who during the past 2 years have met DSM IV-R-TR diagnostic criteria for post-traumatic stress disorder, addition of ethanol and methaqualone to exclusion criterion #8, modification of exclusion criterion #12 to exclude patients with a C-SSRS evaluation of type 4 or 5 within the last 6 months of screening or randomization, deletion of sub-criterion regarding insulin use in exclusion criterion #15, addition of laboratory values that signify a major medical illness that is inadequately controlled to exclusion criterion #18, exclusion criterion # 21 was revised to not limit the exclusions to hospitalizations for MDD only, addition of an exclusion criterion (#22) to clarify that a failed SAFER interview excludes a patient from participating in the study.
25 October 2012	Increase in the number of study sites, clarification that, to be eligible for the study, patients' lifetime history of inadequate response to 3 or more antidepressant treatments must include the current antidepressant medication, exclusion criterion #11 was revised to allow for repeat testing, addition of a new exclusion criterion to exclude patients with a current diagnosis of sleep apnea, addition of a new exclusion criterion to exclude patients with a BMI ≥ 45 kg/m ² , removal of the SAFER interview, removal of the 8-week observation period, addition of a 14-day follow-up visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported