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Result Point of Contact

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Certain Agreements

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is more than 60 days but less than or equal to 180 days from the time submitted to the sponsor for review. The sponsor cannot require changes to the communication and cannot extend the embargo.

Participant Flow

Recruitment Details	This multicenter study was conducted in the US and India between 15 June 2010 and 31 January 2012.
Pre-assignment Details	The study had an up to 21-day screening/washout period, and an 8-week prospective open-label antidepressant treatment (ADT) period to identify the target patient population of inadequate responders to ADT (<50% reduction in HAMD-17 total score during the prospective open-label ADT period, a HAMD-17 total score of ≥16 and a CGI-S score ≥4).

Period: Overall Study

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID	**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID	**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	**Total** *(=sum per row)*
Started	160	160	160	161	641 *(calculated)*
Received treatment	160	158	158	160	636 *(calculated)*
Completed	127	116	110	129	482 *(calculated)*
Not Completed: *(=Started - Completed)*	33 *(calculated)*	44 *(calculated)*	50 *(calculated)*	32 *(calculated)*	159 *(calculated)*
Reason for Not Completed					
Total: *(=sum per column)*	33 *(calculated)*	44 *(calculated)*	50 *(calculated)*	32 *(calculated)*	159 *(calculated)*
Withdrawal by Subject	7	7	7	7	28 *(calculated)*
Other Eligibility criteria not fulfilled	0	1	2	1	4 *(calculated)*
Adverse Event	3	9	21	7	40 *(calculated)*
Other Severe non-compliance to protocol	6	7	4	3	20 *(calculated)*
Other Condition under investigation worsened	1	1	0	0	2 *(calculated)*
Lack of Efficacy	2	2	0	4	8 *(calculated)*
Other Study-specific withdrawal criteria	4	3	1	2	10 *(calculated)*
Lost to Follow-up	4	9	11	8	32 *(calculated)*
Other Not specified	5	5	4	0	14 *(calculated)*
Death	1	0	0	0	1 *(calculated)*

Baseline Characteristics

Overall Number of Baseline Participants					
	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID	**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID	**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	**Total(=sum across Arm/Groups)**
Overall Number of Baseline Participants	160	160	160	161	641 *(calculated)*

Baseline Analysis Population Description	

Age Continuous (Units: years)

Mean
Standard Deviation

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID	**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID	**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	**Total**
	40.6 (11.78)	42.1 (11.77)	42.1 (11.35)	43.2 (11.92)	42.0 (11.72)

Gender, Male/Female (Units: participants)

Number
Not Applicable

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID	**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID	**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	**Total** *(=sum per row)*
Female	85	91	93	96	365 *(calculated)*
Male	75	69	67	65	276 *(calculated)*

Race/Ethnicity, Customized (Units: participants)

Number
Not Applicable

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID	**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID	**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	**Total** *(=sum per row)*
White	87	100	91	103	381 *(calculated)*
Black or African American	20	23	27	14	84 *(calculated)*
Asian	50	35	40	42	167 *(calculated)*
Native Hawaiian or other Pacific Islander	0	0	0	1	1 *(calculated)*
American Indian or Alaska Native	0	1	0	0	1 *(calculated)*
Other	3	1	2	1	7 *(calculated)*

Study Specific Characteristic [Hamilton Rating Scale for Depression-17 items (HAMD-17) total score at randomization] (Units: Scores on a scale)
A 17-item, clinician-rated scale that assesses depressive symptoms. The HAMD-17 consists of 17 symptoms, each of which is rated from 0 to 2 or 0 to 4, where 0 is none/absent. The HAMD-17 total score is calculated as the sum of the 17 individual symptom scores; the total score can range from 0 to 52. Higher HAMD-17 scores indicate more severe depression.
Mean
Standard Deviation

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID	**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID	**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	**Total**
	22.3 (3.98)	21.5 (3.74)	22.0 (4.07)	22.1 (4.08)	22.0 (3.97)

Study Specific Characteristic [Montgomery-Asberg Depression Rating Scale (MADRS) total score at randomization] (Units: Scores on a scale)
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.
Mean
Standard Deviation

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID	**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID	**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	**Total**
	26.86 (6.331)	26.37 (6.036)	27.06 (5.854)	26.70 (6.809)	26.75 (6.261)

Outcome Measures

Expand All

1. Primary: Change in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from randomization to end of treatment.

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.
Time Frame:	Randomization (Week 8) to end of treatment (Week 16)
Safety Issue:	No
Analysis Population Description:	Modified intent-to-treat analysis set including all randomized patients who received at least 1 dose of investigational product (TC-5214 or placebo) and who had a randomization and at least 1 post-randomization MADRS total score.

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID	**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID	**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID
Number of Participants Analyzed:	155	156	152	157

Change in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from randomization to end of treatment. Units: units on a scale	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error
	-12.1	0.81	-11.8	0.83	-11.3	0.84	-11.2	0.80

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	Mixed model repeated measures (MMRM) includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization MADRS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	1.000	The adjusted p-value protects the overall family-wise error rate by taking into account the multiple comparisons between the TC-5214 doses for both the primary efficacy variable (MADRS) and the key secondary efficacy variable (SDS).
Method	Other MMRM	
Other LS mean	-0.9	
Standard Error of the mean	1.07	
95% Confidence Interval 2-Sided	-2.96 to 1.24	

Statistical Analysis		
Groups	2 mg BID TC-5214, Placebo	Mixed model repeated measures (MMRM) includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization MADRS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	1.000	
Method	Other MMRM	
Other LS mean	-0.6	
Standard Error of the mean	1.08	
95% Confidence Interval 2-Sided	-2.67 to 1.57	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	Mixed model repeated measures (MMRM) includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization MADRS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	1.000	
Method	Other MMRM	
Other LS mean	-0.1	
Standard Error of the mean	1.09	
95% Confidence Interval 2-Sided	-2.26 to 2.04	

2. Secondary: Response in depressive symptoms of major depressive disorder (MDD), defined as a ≥50% reduction from randomization (Week 8) in MADRS total score at end of treatment

Description: The percentage of patients with a ≥50% reduction from randomization (Week 8) in MADRS total score at end of treatment (Week 16) was calculated.

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.

Time Frame: Randomization (Week 8) to end of treatment (Week 16)

Safety Issue: No

Analysis Population Description: Modified intent-to-treat analysis set including all randomized patients who received at least 1 dose of investigational product (TC-5214 or placebo) and who had a randomization and at least 1 post-randomization MADRS total score.

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID	**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID	**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID

Number of Participants Analyzed:	155	156	152	157
Response in depressive symptoms of major depressive disorder (MDD), defined as a ≥50% reduction from randomization (Week 8) in MADRS total score at end of treatment (Week 16) Units: percentage of participants analyzed	Number	Number	Number	Number
	43.9	39.7	38.8	42.7

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	Logistic regression model including treatment and pooled center as fixed effects and the randomization MADRS total score as a covariate.
Non-Inferiority/Equivalence Test	No	
P Value	0.967	
Method	Regression, Logistic	
Odds Ratio (OR)	1.01	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.24	
95% Confidence Interval 2-Sided	0.64 to 1.60	

Statistical Analysis		
Groups	2 mg BID TC-5214, Placebo	Logistic regression model including treatment and pooled center as fixed effects and the randomization MADRS total score as a covariate.
Non-Inferiority/Equivalence Test	No	
P Value	0.670	
Method	Regression, Logistic	
Odds Ratio (OR)	0.90	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.21	
95% Confidence Interval 2-Sided	0.57 to 1.43	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	Logistic regression model including treatment and pooled center as fixed effects and the randomization MADRS total score as a covariate.
Non-Inferiority/Equivalence Test	No	
P Value	0.544	
Method	Regression, Logistic	
Odds Ratio (OR)	0.87	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.21	
95% Confidence Interval 2-Sided	0.54 to 1.38	

3. Secondary: Remission in depressive symptoms of MDD, defined as MADRS total score of ≤8 at end of treatment (Week 16)

Description: The percentage of patients with a MADRS total score of ≤8 at end of treatment (Week 16) was calculated.

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.

Time Frame: Week 16

Safety Issue: No

Analysis Population Description: Modified intent-to-treat analysis set including all randomized patients who received at least 1 dose of investigational product (TC-5214 or placebo) and who had a randomization and at least 1 post-randomization MADRS total score.

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID	**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID	**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID
Number of Participants Analyzed:	155	156	152	157
Remission in depressive symptoms of MDD, defined as MADRS total score of ≤8 at end of treatment (Week 16) Units: percentage of participants analyzed	Number	Number	Number	Number
	29.0	26.9	23.7	29.9

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	Logistic regression model including treatment and pooled center as fixed effects and the

		randomization MADRS total score as a covariate.
Non-Inferiority/Equivalence Test	No	
P Value	0.730	
Method	Regression, Logistic	
Odds Ratio (OR)	0.91	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.24	
95% Confidence Interval 2-Sided	0.55 to 1.53	

Statistical Analysis		
Groups	2 mg BID TC-5214, Placebo	Logistic regression model including treatment and pooled center as fixed effects and the randomization MADRS total score as a covariate.
Non-Inferiority/Equivalence Test	No	
P Value	0.671	
Method	Regression, Logistic	
Odds Ratio (OR)	0.89	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.23	
95% Confidence Interval 2-Sided	0.53 to 1.50	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	Logistic regression model including treatment and pooled center as fixed effects and the randomization MADRS total score as a covariate.
Non-Inferiority/Equivalence Test	No	
P Value	0.308	
Method	Regression, Logistic	
Odds Ratio (OR)	0.76	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.20	
95% Confidence Interval 2-Sided	0.45 to 1.29	

4. Secondary: Early and Sustained Response, defined as a ≥50% reduction from randomization (Week 8) in MADRS total score and a MADRS total score of ≤12 at Week 10, Week 12, Week

Description: The percentage of patients with a ≥50% reduction from randomization (Week 8) in MADRS total score and a MADRS total score of ≤12 at Week 10, Week 12, Week 14, and end of treatment (Week 16) was calculated.

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.

Time Frame: Randomization (Week 8) to end of treatment (Week 16); Week 10, Week 12, Week 14, and Week 16

Safety Issue: No

Analysis Population Description: Modified intent-to-treat analysis set including all randomized patients who received at least 1 dose of investigational product (TC-5214 or placebo) and who had a randomization and at least 1 post-randomization MADRS total score.

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID	**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID	**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID
Number of Participants Analyzed:	148	153	145	153
Early and Sustained Response, defined as a ≥50% reduction from randomization (Week 8) in MADRS total score and a MADRS total score of ≤12 at Week 10, Week 12, Week 14, and end of treatment (Week 16) Units: percentage of participants analyzed	Number	Number	Number	Number
	8.8	7.8	8.3	8.5

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	Logistic regression model including treatment and pooled center as fixed effects and the randomization MADRS total score as a covariate.
Non-Inferiority/Equivalence Test	No	
P Value	0.905	
Method	Regression, Logistic	
Odds Ratio (OR)	0.95	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.40	
95% Confidence Interval 2-Sided	0.42 to 2.15	

Statistical Analysis

Groups	2 mg BID TC-5214, Placebo	Logistic regression model including treatment and pooled center as fixed effects and the randomization MADRS total score as a covariate.
Non-Inferiority/Equivalence Test	No	
P Value	0.864	
Method	Regression, Logistic	
Odds Ratio (OR)	0.93	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.39	
95% Confidence Interval 2-Sided	0.41 to 2.14	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	Logistic regression model including treatment and pooled center as fixed effects and the randomization MADRS total score as a covariate.
Non-Inferiority/Equivalence Test	No	
P Value	0.958	
Method	Regression, Logistic	
Odds Ratio (OR)	0.98	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.42	
95% Confidence Interval 2-Sided	0.43 to 2.25	

5. Secondary: Sustained Response, defined as a ≥50% reduction from randomization (Week 8) in MADRS total score and a MADRS total score of ≤12 at Week 12, Week 14, and end of treat

Description: The percentage of patients with a ≥50% reduction from randomization (Week 8) in MADRS total score and a MADRS total score of ≤12 at Week 12, Week 14, and end of treatment (Week 16) was calculated.

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.

Time Frame: Randomization (Week 8) to end of treatment (Week 16); Week 12, Week 14, and Week 16

Safety Issue: No

Analysis Population Description: Modified intent-to-treat analysis set including all randomized patients who received at least 1 dose of investigational product (TC-5214 or placebo) and who had a randomization and at least 1 post-randomization MADRS total score.

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID	**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID	**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID
Number of Participants Analyzed:	145	150	143	151
Sustained Response, defined as a ≥50% reduction from randomization (Week 8) in MADRS total score and a MADRS total score of ≤12 at Week 12, Week 14, and end of treatment (Week 16) Units: percentage of patients analyzed	Number	Number	Number	Number
	15.9	18.7	14.0	15.9

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	Logistic regression model including treatment and pooled center as fixed effects and the randomization MADRS total score as a covariate.
Non-Inferiority/Equivalence Test	No	
P Value	0.778	
Method	Regression, Logistic	
Odds Ratio (OR)	0.91	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.30	
95% Confidence Interval 2-Sided	0.48 to 1.73	

Statistical Analysis		
Groups	2 mg BID TC-5214, Placebo	Logistic regression model including treatment and pooled center as fixed effects and the randomization MADRS total score as a covariate.
Non-Inferiority/Equivalence Test	No	
P Value	0.532	
Method	Regression, Logistic	
Odds Ratio (OR)	1.22	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.38	
95% Confidence Interval 2-Sided	0.66 to 2.24	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	Logistic regression model including treatment and pooled center as fixed effects and the randomization MADRS total score as a covariate.
Non-Inferiority/Equivalence Test	No	
P Value	0.633	
Method	Regression, Logistic	
Odds Ratio (OR)	0.85	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.29	
95% Confidence Interval 2-Sided	0.44 to 1.64	

6. Secondary: Sustained Remission, defined as a MADRS total score of ≤8 at Week 12, Week 14, and end of treatment (Week 16)

Description: The percentage of patients with a MADRS total score of ≤8 at Week 12, Week 14, and end of treatment (Week 16)was calculated.

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.

Time Frame: Week 12, Week 14, Week 16

Safety Issue: No

Analysis Population Description: Modified intent-to-treat analysis set including all randomized patients who received at least 1 dose of investigational product (TC-5214 or placebo) and who had a randomization and at least 1 post-randomization MADRS total score.

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID	**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID	**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID
Number of Participants Analyzed:	146	150	144	152
Sustained Remission, defined as a MADRS total score of ≤8 at Week 12, Week 14, and end of treatment (Week 16) Units: percentage of participants analyzed	Number	Number	Number	Number
	10.3	12.7	7.6	9.2

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	Logistic regression model including treatment and pooled center as fixed effects and the randomization MADRS total score as a covariate.
Non-Inferiority/Equivalence Test	No	
P Value	0.949	
Method	Regression, Logistic	
Odds Ratio (OR)	1.03	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.42	
95% Confidence Interval 2-Sided	0.46 to 2.31	

Statistical Analysis		
Groups	2 mg BID TC-5214, Placebo	Logistic regression model including treatment and pooled center as fixed effects and the randomization MADRS total score as a covariate.
Non-Inferiority/Equivalence Test	No	
P Value	0.253	
Method	Regression, Logistic	
Odds Ratio (OR)	1.57	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.62	
95% Confidence Interval 2-Sided	0.72 to 3.40	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	Logistic regression model including treatment and pooled center as fixed effects and the randomization MADRS total score as a covariate.
Non-Inferiority/Equivalence Test	No	
P Value	0.763	
Method	Regression, Logistic	
Odds Ratio (OR)	0.88	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.39	
95% Confidence Interval 2-Sided	0.37 to 2.08	

7. Secondary: Change in depressive symptoms from randomization (Week 8) to end of treatment (Week 16) as measured by Hamilton Rating Scale for Depression-17 items (HAMD-17) tota

Description: A 17-item, clinician-rated scale that assesses depressive symptoms. The HAMD-17 consists of 17 symptoms, each of which is rated from 0 to 2 or 0 to 4, where 0 is none/absent. The HAMD-17 total score is calculated as the sum of the 17 individual symptom scores; the total score can range from 0 to 52. Higher HAMD-17 scores indicate more severe depression.

Time Frame: Randomization (Week 8) to end of treatment (Week 16)

Safety Issue: No

Analysis Population Description: Modified intent-to-treat analysis set including all randomized patients who received at least 1 dose of investigational product (TC-5214 or placebo) and who had a randomization and at least 1 post-randomization MADRS total score.

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID		**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID		**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	147		144		142		150	
Change in depressive symptoms from randomization (Week 8) to end of treatment (Week 16) as measured by Hamilton Rating Scale for Depression-17 items (HAMD-17) total score Units: units on a scale	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error
	-10.1	0.79	-9.7	0.79	-9.5	0.79	-9.1	0.78

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	Analysis of covariance (ANCOVA) with randomization HAMD-17 total score as covariate, treatment as a fixed effect and pooled center as a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.207	
Method	ANCOVA	
Other LS mean	-1.0	
Standard Error of the mean	0.78	
95% Confidence Interval 2-Sided	-2.51 to 0.55	

Statistical Analysis		
Groups	2 mg BID TC-5214, Placebo	Analysis of covariance (ANCOVA) with randomization HAMD-17 total score as covariate, treatment as a fixed effect and pooled center as a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.427	
Method	ANCOVA	
Other LS mean	-0.6	
Standard Error of the mean	0.78	
95% Confidence Interval 2-Sided	-2.16 to 0.91	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	Analysis of covariance (ANCOVA) with randomization HAMD-17 total score as covariate, treatment as a fixed effect and pooled center as a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.591	
Method	ANCOVA	
Other LS mean	-0.4	
Standard Error of the mean	0.78	
95% Confidence Interval 2-Sided	-1.96 to 1.12	

8. Secondary: Change in the clinician-rated global outcome of severity as measured by the Clinical Global Impression-Severity (CGI-S) score from randomization (Week 8) to end of treatme

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. Higher CGI-S scores indicate greater illness severity.

Time Frame: Randomization (Week 8) to end of treatment (Week 16)

Safety Issue: No

Analysis Population Description: Modified intent-to-treat analysis set including all randomized patients who received at least 1 dose of investigational product (TC-5214 or placebo) and who had a randomization and at least 1 post-randomization MADRS total score.

	0.5 mg BID TC-5214	**2 mg BID TC-5214**	**4 mg BID TC-5214**	**Placebo**

	Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID		Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID		Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID		Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	155		156		152		157	
Change in the clinician-rated global outcome of severity as measured by the Clinical Global Impression-Severity (CGI-S) score from randomization (Week 8) to end of treatment (Week 16) Units: units on a scale	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error
	-1.3	0.10	-1.3	0.11	-1.2	0.11	-1.2	0.10

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit, and treatment by visit interaction as explanatory variables and the randomization CGI-S total score as a covariate. Treatment, visit, and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.551	
Method	Other MMRM	
Other LS mean	-0.1	
Standard Error of the mean	0.13	
95% Confidence Interval	-0.34 to 0.18	

Statistical Analysis		
Groups	2 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit, and treatment by visit interaction as explanatory variables and the randomization CGI-S total score as a covariate. Treatment, visit, and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.487	
Method	Other MMRM	
Other LS mean	-0.1	
Standard Error of the mean	0.13	
95% Confidence Interval 2-Sided	-0.36 to 0.17	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit, and treatment by visit interaction as explanatory variables and the randomization CGI-S total score as a covariate. Treatment, visit, and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.780	
Method	Other MMRM	
Other LS mean	0.0	
Standard Error of the mean	0.14	
95% Confidence Interval 2-Sided	-0.23 to 0.31	

9. Secondary: Response in the Clinical Global Impression-Improvement (CGI-I) defined as CGI-I rating of "very much improved" or "much improved" from randomization (Week 8) to end of

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.

Time Frame: Randomization (Week 8) to end of treatment (Week 16)

Safety Issue: No

Analysis Population Description: Modified intent-to-treat analysis set including all randomized patients who received at least 1 dose of investigational product (TC-5214 or placebo) and who had a randomization and at least 1 post-randomization MADRS total score.

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor	**2 mg BID TC-5214** Selective serotonin reuptake inhibitor	**4 mg BID TC-5214** Selective serotonin reuptake inhibitor	**Placebo** Selective serotonin reuptake inhibitor

	(SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID	(SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID	(SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID	(SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID
Number of Participants Analyzed:	155	156	152	157
Response in the Clinical Global Impression-Improvement (CGI-I) defined as CGI-I rating of "very much improved" or "much improved" from randomization (Week 8) to end of treatment (Week 16) Units: percentage of participants analyzed	Number	Number	Number	Number
	48.4	49.4	37.5	47.8

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	Logistic regression model including treatment and pooled center as fixed effects and the randomization Clinical Global Impression Severity (CGI-S) as a covariate.
Non-Inferiority/Equivalence Test	No	
P Value	0.908	
Method	Regression, Logistic	
Odds Ratio (OR)	0.97	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.23	
95% Confidence Interval 2-Sided	0.62 to 1.53	

Statistical Analysis		
Groups	2 mg BID TC-5214, Placebo	Logistic regression model including treatment and pooled center as fixed effects and the randomization Clinical Global Impression Severity (CGI-S) as a covariate.
Non-Inferiority/Equivalence Test	No	
P Value	0.803	
Method	Regression, Logistic	
Odds Ratio (OR)	1.06	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.24	
95% Confidence Interval 2-Sided	0.67 to 1.67	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	Logistic regression model including treatment and pooled center as fixed effects and the randomization Clinical Global Impression Severity (CGI-S) as a covariate.
Non-Inferiority/Equivalence Test	No	
P Value	0.066	
Method	Regression, Logistic	
Odds Ratio (OR)	0.65	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.15	
95% Confidence Interval 2-Sided	0.41 to 1.03	

10. Secondary: Change in Hamilton Anxiety Scale (HAM-A) total score from randomization (Week 8) to end of treatment (Week 16)

Description: A 14-item clinician-administered scale for the evaluation of anxiety symptoms. Each HAM-A item is rated on a 0 to 4 scale, the total score can range from 0 to 56. Higher HAM-A scores indicate higher levels of anxiety.

Time Frame: Randomization (Week 8) to end of treatment (Week 16)

Safety Issue: No

Analysis Population Description:

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID		**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID		**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	147		144		142		150	
Change in Hamilton Anxiety Scale (HAM-A) total score from randomization (Week 8) to end of treatment (Week 16) Units: units on a scale	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error
	-7.07	0.648	-6.46	0.652	-6.75	0.655	-6.24	0.641

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	An analysis of covariance (ANCOVA) with randomization HAM-A total score as covariate, treatment as a fixed effect and pooled center as a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.202	
Method	ANCOVA	
Other LS mean	-0.82	
Standard Error of the mean	0.645	
95% Confidence Interval 2-Sided	-2.091 to 0.442	

Statistical Analysis		
Groups	2 mg BID TC-5214, Placebo	An analysis of covariance (ANCOVA) with randomization HAM-A total score as covariate, treatment as a fixed effect and pooled center as a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.738	
Method	ANCOVA	
Other LS mean	-0.22	
Standard Error of the mean	0.647	
95% Confidence Interval 2-Sided	-1.487 to 1.055	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	An analysis of covariance (ANCOVA) with randomization HAM-A total score as covariate, treatment as a fixed effect and pooled center as a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.433	
Method	ANCOVA	
Other LS mean	-0.51	
Standard Error of the mean	0.650	
95% Confidence Interval 2-Sided	-1.787 to 0.767	

11. Secondary: Change in MADRS total score from randomization (Week 8) to Week 9

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.

Time Frame: Randomization (Week 8) to Week 9

Safety Issue: No

Analysis Population Description: Modified intent-to-treat analysis set including all randomized patients who received at least 1 dose of investigational product (TC-5214 or placebo) and who had a randomization and at least 1 post-randomization MADRS total score.

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID		**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID		**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	152		150		146		152	
Change in MADRS total score from randomization (Week 8) to Week 9 Units: units on a scale	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error
	-4.0	0.52	-5.1	0.52	-4.0	0.52	-5.0	0.52

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization MADRS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.097	
Method	Other MMRM	
Other LS mean	1.0	

Standard Error of the mean	0.61	
95% Confidence Interval 2-Sided	-0.18 to 2.22	

Statistical Analysis		
Groups	2 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization MADRS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.882	
Method	Other MMRM	
Other LS mean	-0.1	
Standard Error of the mean	0.61	
95% Confidence Interval 2-Sided	-1.29 to 1.11	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization MADRS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.100	
Method	Other MMRM	
Other LS mean	1.0	
Standard Error of the mean	0.62	
95% Confidence Interval 2-Sided	-0.19 to 2.23	

12. Secondary: Change in MADRS Total Score From Randomization (Week 8) to Week 10

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.

Time Frame: Randomization (Week 8) to Week 10

Safety Issue: No

Analysis Population Description: Modified intent-to-treat analysis set including all randomized patients who received at least 1 dose of investigational product (TC-5214 or placebo) and who had a randomization and at least 1 post-randomization MADRS total score.

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID		**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID		**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	150		146		139		148	
Change in MADRS Total Score From Randomization (Week 8) to Week 10 Units: units on a scale	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error
	-6.3	0.60	-6.9	0.60	-7.3	0.61	-7.1	0.60

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization MADRS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.303	
Method	Other MMRM	
Other LS mean	0.8	
Standard Error of the mean	0.74	
95% Confidence Interval 2-Sided	-0.69 to 2.22	

Statistical Analysis		
Groups	2 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled

		center, visit and treatment by visit interaction as explanatory variables and the randomization MADRS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.793	
Method	Other MMRM	
Other LS mean	0.2	
Standard Error of the mean	0.74	
95% Confidence Interval 2-Sided	-1.26 to 1.65	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization MADRS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.762	
Method	Other MMRM	
Other LS mean	-0.2	
Standard Error of the mean	0.75	
95% Confidence Interval 2-Sided	-1.70 to 1.25	

13. Secondary: Change in MADRS total score from randomization (Week 8) to Week 12

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.

Time Frame: Randomization (Week 8) to Week 12

Safety Issue: No

Analysis Population Description: Modified intent-to-treat analysis set including all randomized patients who received at least 1 dose of investigational product (TC-5214 or placebo) and who had a randomization and at least 1 post-randomization MADRS total score.

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID		**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID		**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	142		135		128		145	
Change in MADRS total score from randomization (Week 8) to Week 12 Units: units on a scale	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error
	-9.4	0.70	-9.4	0.71	-8.9	0.73	-8.5	0.70

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization MADRS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.339	
Method	Other MMRM	
Other LS mean	-0.9	
Standard Error of the mean	0.91	
95% Confidence Interval 2-Sided	-2.65 to 0.92	

Statistical Analysis		
Groups	2 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization MADRS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model;

		pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.321	
Method	Other MMRM	
Other LS mean	-0.9	
Standard Error of the mean	0.91	
95% Confidence Interval 2-Sided	-2.70 to 0.89	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization MADRS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.680	
Method	Other MMRM	
Other LS mean	-0.4	
Standard Error of the mean	0.92	
95% Confidence Interval 2-Sided	-2.20 to 1.43	

14. Secondary: Change in MADRS total score from randomization (Week 8) to Week 14

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.

Time Frame: Randomization (Week 8) to Week 14

Safety Issue: No

Analysis Population Description: Modified intent-to-treat analysis set including all randomized patients who received at least 1 dose of investigational product (TC-5214 or placebo) and who had a randomization and at least 1 post-randomization MADRS total score.

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID		**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID		**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	140		127		119		134	
Change in MADRS total score from randomization (Week 8) to Week 14 Units: units on a scale	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error
	-11.0	0.74	-11.3	0.76	-10.6	0.77	-10.7	0.74

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization MADRS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.737	
Method	Other MMRM	
Other LS mean	-0.3	
Standard Error of the mean	0.97	
95% Confidence Interval 2-Sided	-2.23 to 1.58	

Statistical Analysis		
Groups	2 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization MADRS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.547	

Method	Other MMRM	
Other LS mean	-0.6	
Standard Error of the mean	0.98	
95% Confidence Interval 2-Sided	-2.52 to 1.33	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization MADRS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.953	
Method	Other MMRM	
Other LS mean	0.1	
Standard Error of the mean	0.99	
95% Confidence Interval 2-Sided	-1.89 to 2.01	

15. Secondary: Change in functional impairment from randomization (Week 8) to end of treatment (Week 16) as measured by the Sheehan Disability Scale (SDS) total score

Description: Sheehan Disability Scale (SDS) is 5-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 inter-correlated domains (school/work, social life, and family life/home responsibilities) and ranges from 0 (unimpaired) to 30 (highly impaired).

Time Frame: Randomization (Week 8) to end of treatment (Week 16)

Safety Issue: No

Analysis Population Description: Modified intent-to-treat analysis set including all randomized patients who received at least 1 dose of investigational product (TC-5214 or placebo) and who had a randomization and at least 1 post-randomization MADRS total score.

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID		**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID		**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	152		148		149		153	
Change in functional impairment from randomization (Week 8) to end of treatment (Week 16) as measured by the Sheehan Disability Scale (SDS) total score Units: units on a scale	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error
	-5.53	0.631	-5.45	0.643	-4.53	0.651	-4.93	0.627

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit, and treatment by visit interaction as explanatory variables and the randomization SDS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	1.000	The adjusted p-value protects the overall family-wise error rate by taking into account the multiple comparisons between the TC-5214 doses for both the primary efficacy variable (MADRS) and the key secondary efficacy variable (SDS).
Method	Other MMRM	
Other LS mean	-0.60	
Standard Error of the mean	0.746	
95% Confidence Interval 2-Sided	-2.069 to 0.864	

Statistical Analysis		
Groups	2 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit, and treatment by visit interaction as explanatory variables and the randomization SDS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.

Non-Inferiority/Equivalence Test	No	
P Value	1.000	The adjusted p-value protects the overall family-wise error rate by taking into account the multiple comparisons between the TC-5214 doses for both the primary efficacy variable (MADRS) and the key secondary efficacy variable (SDS).
Method	Other MMRM	
Other LS mean	-0.52	
Standard Error of the mean	0.755	
95% Confidence Interval 2-Sided	-2.004 to 0.960	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit, and treatment by visit interaction as explanatory variables and the randomization SDS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	1.000	The adjusted p-value protects the overall family-wise error rate by taking into account the multiple comparisons between the TC-5214 doses for both the primary efficacy variable (MADRS) and the key secondary efficacy variable (SDS).
Method	Other MMRM	
Other LS mean	0.40	
Standard Error of the mean	0.761	
95% Confidence Interval 2-Sided	-1.095 to 1.896	

16. Secondary: Change in functional impairment from randomization (Week 8) to end of treatment (Week 16) as measured by SDS work/school domain score

Description: A 5-item, self-administered scale that measures the extent a patient is impaired by their disease. Higher scores indicate more severe impairment. The 3 inter-correlated domains are school/work, social life, and family life/home responsibilities. The numerical rating for the work/school domain score is 0- 10, where 10 is considered to be 'highly impaired'.

Time Frame: Randomization (Week 8) to end of treatment (Week 16)

Safety Issue: No

Analysis Population Description: Modified intent-to-treat analysis set including all randomized patients who received at least 1 dose of investigational product (TC-5214 or placebo) and who had a randomization and at least 1 post-randomization MADRS total score.

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID		**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID		**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	132		123		134		137	
Change in functional impairment from randomization (Week 8) to end of treatment (Week 16) as measured by SDS work/school domain score Units: units on a scale	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error
	-1.7	0.21	-1.8	0.22	-1.7	0.21	-1.7	0.21

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization SDS work/school domain score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.953	
Method	Other MMRM	
Other LS mean	0.0	
Standard Error of the mean	0.29	
95% Confidence Interval 2-Sided	-0.56 to 0.59	

Statistical Analysis

Groups	2 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization SDS work/school domain score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.868	
Method	Other MMRM	
Other LS mean	0.0	
Standard Error of the mean	0.30	
95% Confidence Interval 2-Sided	-0.64 to 0.54	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization SDS work/school domain score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.792	
Method	Other MMRM	
Other LS mean	0.1	
Standard Error of the mean	0.30	
95% Confidence Interval 2-Sided	-0.50 to 0.66	

17. Secondary: Change in functional impairment from randomization (Week 8) to end of treatment (Week 16) as measured by SDS social life domain score

Description: A 5-item, self-administered scale that measures the extent a patient is impaired by their disease. Higher scores indicate more severe impairment. The 3 inter-correlated domains are school/work, social life, and family life/home responsibilities. The numerical rating for the SDS social life domain score is 0- 10, where 10 is considered to be 'highly impaired'.

Time Frame: Randomization (Week 8) to end of treatment (Week 16)

Safety Issue: No

Analysis Population Description: Modified intent-to-treat analysis set including all randomized patients who received at least 1 dose of investigational product (TC-5214 or placebo) and who had a randomization and at least 1 post-randomization MADRS total score.

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID		**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID		**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	152		148		149		153	
Change in functional impairment from randomization (Week 8) to end of treatment (Week 16) as measured by SDS social life domain score Units: units on a scale	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error
	-1.9	0.22	-1.9	0.23	-1.6	0.23	-1.9	0.22

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization SDS social life domain score. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.915	
Method	Other MMRM	
Other LS mean	0.0	
Standard Error of the mean	0.26	
95% Confidence Interval 2-Sided	-0.54 to 0.48	

Statistical Analysis		
Groups	2 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction

		as explanatory variables and the randomization SDS social life domain score. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.972	
Method	Other MMRM	
Other LS mean	0.0	
Standard Error of the mean	0.26	
95% Confidence Interval 2-Sided	-0.51 to 0.53	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization SDS social life domain score. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.237	
Method	Other MMRM	
Other LS mean	0.3	
Standard Error of the mean	0.27	
95% Confidence Interval 2-Sided	-0.21 to 0.84	

18. Secondary: Change in functional impairment from randomization (Week 8) to end of treatment (Week 16) as measured by SDS family life/home responsibilities domain score

Description: A 5-item, self-administered scale that measures the extent a patient is impaired by their disease. Higher scores indicate more severe impairment. The 3 inter-correlated domains are school/work, social life, and family life/home responsibilities. The numerical rating for the SDS family life/home responsibilities domain score is 0- 10, where 10 is considered to be 'highly impaired'.

Time Frame: Randomization (Week 8) to end of treatment (Week 16)

Safety Issue: No

Analysis Population Description: Modified intent-to-treat analysis set including all randomized patients who received at least 1 dose of investigational product (TC-5214 or placebo) and who had a randomization and at least 1 post-randomization MADRS total score.

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID		**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID		**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	152		148		149		153	
Change in functional impairment from randomization (Week 8) to end of treatment (Week 16) as measured by SDS family life/home responsibilities domain score Units: units on a scale	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error
	-1.9	0.22	-1.8	0.23	-1.6	0.23	-1.6	0.22

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization SDS family life/home responsibilities domain score. Treatment, visit and treatment by visit interaction are effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.213	
Method	Other MMRM	
Other LS mean	-0.3	
Standard Error of the mean	0.27	
95% Confidence Interval 2-Sided	-0.87 to 0.19	

Statistical Analysis		
Groups	2 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as

		explanatory variables and the randomization SDS family life/home responsibilities domain score. Treatment, visit and treatment by visit interaction are effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.343	
Method	Other MMRM	
Other LS mean	-0.3	
Standard Error of the mean	0.27	
95% Confidence Interval 2-Sided	-0.80 to 0.28	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization SDS family life/home responsibilities domain score. Treatment, visit and treatment by visit interaction are effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.971	
Method	Other MMRM	
Other LS mean	0.0	
Standard Error of the mean	0.28	
95% Confidence Interval 2-Sided	-0.55 to 0.53	

19. Secondary: Change in overall quality of life and satisfaction from randomization (Week 8) to end of treatment (Week 16) by assessing the Quality of Life Enjoyment and Satisfaction Que

Description: The Q-LES-Q-SF total score is derived by summing item scores 1 to 14. Higher scores are indicative of greater enjoyment or satisfaction in each domain. The Q-LES-Q-SF % maximum total score is calculated as 100% × (Q-LES-Q-SF total score – 14) / 56, and can range from 0% to 100%.

Time Frame: Randomization (Week 8) to end of treatment (Week 16)

Safety Issue: No

Analysis Population Description: Modified intent-to-treat analysis set including all randomized patients who received at least 1 dose of investigational product (TC-5214 or placebo) and who had a randomization and at least 1 post-randomization MADRS total score.

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID		**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID		**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	152		148		144		151	
Change in overall quality of life and satisfaction from randomization (Week 8) to end of treatment (Week 16) by assessing the Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) % maximum total score Units: units on a scale	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error
	12.81	1.470	11.42	1.483	8.83	1.499	10.71	1.467

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	ANCOVA with randomization Q-LES-Q-SF % maximum total score as covariate, treatment as a fixed effect and pooled center as a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.215	
Method	ANCOVA	
Other LS mean	2.10	
Standard Error of the mean	1.694	
95% Confidence Interval 2-Sided	-1.224 to 5.431	

Statistical Analysis		
Groups	2 mg BID TC-5214, Placebo	ANCOVA with randomization Q-LES-Q-SF % maximum total score as covariate, treatment as a fixed effect and pooled center as a random effect.

Non-Inferiority/Equivalence Test	No	
P Value	0.673	
Method	ANCOVA	
Other LS mean	0.72	
Standard Error of the mean	1.702	
95% Confidence Interval 2-Sided	-2.624 to 4.062	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	ANCOVA with randomization Q-LES-Q-SF % maximum total score as covariate, treatment as a fixed effect and pooled center as a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.275	
Method	ANCOVA	
Other LS mean	-1.88	
Standard Error of the mean	1.716	
95% Confidence Interval 2-Sided	-5.248 to 1.494	

20. Secondary: Change from randomization (Week 8) to end of treatment (Week 16) in Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form(Q LES-Q-SF)item 15

Description: The Q-LES-Q-SF (Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form) measures the patient's satisfaction with medication and overall quality of life. The 15th item queries respondents' satisfaction with the medication they are taking, rated on a 1 to 4 scale, score 0 indicates that no medication was taken. Higher scores are indicative of greater satisfaction.

Time Frame: Randomization (Week 8) to end of treatment (Week 16)

Safety Issue: No

Analysis Population Description: Modified intent-to-treat analysis set including all randomized patients who received at least 1 dose of investigational product (TC-5214 or placebo) and who had a randomization and at least 1 post-randomization MADRS total score.

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID		**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID		**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	142		136		124		138	
Change from randomization (Week 8) to end of treatment (Week 16) in Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form(Q LES-Q-SF)item 15 Units: units on a scale	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error
	0.3	0.08	0.4	0.08	0.2	0.08	0.4	0.08

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	An analysis of covariance (ANCOVA) with randomization Q-LES-Q-SF item 15 score as covariate, treatment as a fixed effect and pooled center as a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.412	
Method	ANCOVA	
Other LS mean	-0.1	
Standard Error of the mean	0.10	
95% Confidence Interval 2-Sided	-0.28 to 0.11	

Statistical Analysis		
Groups	2 mg BID TC-5214, Placebo	An analysis of covariance (ANCOVA) with randomization Q-LES-Q-SF item 15 score as covariate, treatment as a fixed effect and pooled center as a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.928	
Method	ANCOVA	
Other LS mean	0.0	
Standard Error of the mean	0.10	
95% Confidence Interval 2-Sided	-0.19 to 0.21	

Statistical Analysis

Groups	4 mg BID TC-5214, Placebo	An analysis of covariance (ANCOVA) with randomization Q-LES-Q-SF item 15 score as covariate, treatment as a fixed effect and pooled center as a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.033	
Method	ANCOVA	
Other LS mean	-0.2	
Standard Error of the mean	0.10	
95% Confidence Interval 2-Sided	-0.42 to -0.02	

21. Secondary: Change from randomization (Week 8) to end of treatment (Week 16) in Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q LES-Q-SF) item 16

Description: The Q-LES-Q-SF (Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form) measures the patient's satisfaction with medication and overall quality of life. The 16th item is a global rating of overall life satisfaction and contentment, rated on a 1 to 5 scale. Higher scores are indicative of greater satisfaction.

Time Frame: Randomization (Week 8) to end of treatment (Week 16)

Safety Issue: No

Analysis Population Description: Modified intent-to-treat analysis set including all randomized patients who received at least 1 dose of investigational product (TC-5214 or placebo) and who had a randomization and at least 1 post-randomization MADRS total score.

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID		**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID		**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	152		148		144		151	
Change from randomization (Week 8) to end of treatment (Week 16) in Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q LES-Q-SF) item 16 Units: units on a scale	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error
	0.6	0.08	0.5	0.08	0.4	0.08	0.5	0.08

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	An analysis of covariance (ANCOVA) with randomization Q-LES-Q-SF item 16 as a fixed effect and pooled center as a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.353	
Method	ANCOVA	
Other LS mean	0.1	
Standard Error of the mean	0.10	
95% Confidence Interval 2-Sided	-0.10 to 0.28	

Statistical Analysis		
Groups	2 mg BID TC-5214, Placebo	An analysis of covariance (ANCOVA) with randomization Q-LES-Q-SF item 16 as a fixed effect and pooled center as a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.721	
Method	ANCOVA	
Other LS mean	0.0	
Standard Error of the mean	0.10	
95% Confidence Interval 2-Sided	-0.16 to 0.23	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	An analysis of covariance (ANCOVA) with randomization Q-LES-Q-SF item 16 as a fixed effect and pooled center as a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.666	
Method	ANCOVA	
Other LS mean	0.0	
Standard Error of the mean	0.10	
95% Confidence Interval 2-Sided	-0.24 to 0.15	

22. Secondary: Change in EuroQol - 5 dimensions (EQ-5D) from randomization (Week 8) to end of treatment (Week 16)

Description: A self-assessment questionnaire that provides 2 measures of health status.
The EQ-5D index score is a weighted linear combination over 5 dimensions of
health status. The score for each of the 5 dimensions can range from 1 to 3, and an equation is used to calculate the EQ-5D index score. The EQ-5D index score can range from possible negative values (minimum -0.415) to a maximum of 1.0. The EQ-VAS is a visual analog scale with a range of 0 to 100. For both variables, a higher score indicates a better health state.

Time Frame: Randomization (Week 8) to end of treatment (Week 16)

Safety Issue: No

Analysis Population Description: Modified intent-to-treat analysis set including all randomized patients who received at least 1 dose of investigational product (TC-5214 or placebo) and who had a randomization and at least 1 post-randomization MADRS total score.

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID		**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID		**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	152		147		147		153	
Change in EuroQol - 5 dimensions (EQ-5D) from randomization (Week 8) to end of treatment (Week 16) Units: units on a scale	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error
EQ-5D index score	0.114	0.0169	0.107	0.0173	0.106	0.0176	0.120	0.0168
EQ-5D VAS score	13.4	1.69	12.9	1.73	10.3	1.76	11.5	1.68

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization EQ-5D total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.747	Analysis for change in EQ-5D index score from randomization (Week 8) to end of treatment (Week 16)
Method	Other MMRM	
Other LS mean	-0.006	
Standard Error of the mean	0.0201	
95% Confidence Interval 2-Sided	-0.0459 to 0.0329	

Statistical Analysis		
Groups	2 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization EQ-5D total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.524	Analysis for change in EQ-5D index score from randomization (Week 8) to end of treatment (Week 16)
Method	Other MMRM	
Other LS mean	-0.013	
Standard Error of the mean	0.0203	
95% Confidence Interval 2-Sided	-0.0529 to 0.0270	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization EQ-5D total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.502	Analysis for change in EQ-5D index score from randomization (Week 8) to end of treatment (Week 16)
Method	Other MMRM	

Other LS mean	-0.014	
Standard Error of the mean	0.0206	
95% Confidence Interval 2-Sided	-0.0543 to 0.0267	

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization EQ-5D VAS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.345	Analysis of change in EQ-5D VAS score from randomization (Week 8) to end of treatment (Week 16)
Method	Other MMRM	
Other LS mean	1.9	
Standard Error of the mean	2.06	
95% Confidence Interval 2-Sided	-2.10 to 6.00	

Statistical Analysis		
Groups	2 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization EQ-5D VAS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.486	Analysis of change in EQ-5D VAS score from randomization (Week 8) to end of treatment (Week 16)
Method	Other MMRM	
Other LS mean	1.5	
Standard Error of the mean	2.09	
95% Confidence Interval 2-Sided	-2.65 to 5.56	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit and treatment by visit interaction as explanatory variables and the randomization EQ-5D VAS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.564	Analysis of change in EQ-5D VAS score from randomization (Week 8) to end of treatment (Week 16)
Method	Other MMRM	
Other LS mean	-1.2	
Standard Error of the mean	2.12	
95% Confidence Interval 2-Sided	-5.39 to 2.94	

23. Secondary: Change in Irritability Symptoms as Measured by the Sheehan Irritability Scale (SIS) Total Score From Randomization (Week 8) to End of Treatment (Week 16)

Description: A self-administered scale to be used by clinical subjects to rate suffering over the past week with regard to irritability symptoms. The total SIS score is the sum of 7 items, and ranges from 0 to 70. Each item is assessed on an 11-point scale where 0=not at all, 1-3=mildly, 4-6=moderately, 7-9=markedly, and 10=extremely. The SIS also records the number of days impaired by irritability.

Time Frame: Randomization (Week 8) to end of treatment (Week 16)

Safety Issue: No

Analysis Population Description: Modified intent-to-treat analysis set including all randomized patients who received at least 1 dose of investigational product (TC-5214 or placebo) and who had a randomization and at least 1 post-randomization MADRS total score.

	0.5 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.5 mg BID	**2 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 2 mg BID	**4 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID
Number of Participants	152	148	149	153

Analyzed:								
Change in Irritability Symptoms as Measured by the Sheehan Irritability Scale (SIS) Total Score From Randomization (Week 8) to End of Treatment (Week 16) Units: units on a scale	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error
	-10.2	1.46	-10.1	1.49	-8.3	1.50	-8.8	1.46

Statistical Analysis		
Groups	0.5 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit, and treatment by visit interaction as explanatory variables and the randomization SIS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.350	
Method	Other MMRM	
Other LS mean	-1.4	
Standard Error of the mean	1.55	
95% Confidence Interval 2-Sided	-4.48 to 1.59	

Statistical Analysis		
Groups	2 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit, and treatment by visit interaction as explanatory variables and the randomization SIS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.393	
Method	Other MMRM	
Other LS mean	-1.3	
Standard Error of the mean	1.56	
95% Confidence Interval 2-Sided	-4.41 to 1.73	

Statistical Analysis		
Groups	4 mg BID TC-5214, Placebo	MMRM model includes treatment, pooled center, visit, and treatment by visit interaction as explanatory variables and the randomization SIS total score as a covariate. Treatment, visit and treatment by visit interaction are fixed effects in the model; pooled center is a random effect.
Non-Inferiority/Equivalence Test	No	
P Value	0.745	
Method	Other MMRM	
Other LS mean	0.5	
Standard Error of the mean	1.58	
95% Confidence Interval 2-Sided	-2.59 to 3.62	

Limitations and Caveats

Adverse Events

View Adverse Events