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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 Europe, South Africa, and Latin America between 1 September 2010 and 30 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

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID	**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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	174	174	174	174	696 *(calculated)*
Received treatment	174	174	171	174	693 *(calculated)*
Completed	151	144	125	158	578 *(calculated)*
Not Completed: *(=Started - Completed)*	23 *(calculated)*	30 *(calculated)*	49 *(calculated)*	16 *(calculated)*	118 *(calculated)*
Reason for Not Completed					
Total: *(=sum per column)*	23 *(calculated)*	30 *(calculated)*	49 *(calculated)*	16 *(calculated)*	118 *(calculated)*
Withdrawal by Subject	8	7	15	4	34 *(calculated)*
Other Eligiblity criteria not fulfilled	0	0	2	0	2 *(calculated)*
Adverse Event	10	13	23	3	49 *(calculated)*
Other Severe non-compliance to protocol	0	3	1	3	7 *(calculated)*
Other Condition under investigation worsened	1	1	1	1	4 *(calculated)*
Lack of Efficacy	1	2	2	1	6 *(calculated)*
Other Study-specific withdrawal criteria	0	0	1	2	3 *(calculated)*
Lost to Follow-up	1	1	2	0	4 *(calculated)*
Other Not specified	2	3	2	2	9 *(calculated)*

Baseline Characteristics

Overall Number of Baseline Participants					
	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID	**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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	174	174	174	174	696 *(calculated)*

Baseline Analysis Population Description	

Age Continuous (Units: years)

Mean
Standard Deviation

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID	**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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**
	46.0 (10.66)	45.0 (11.72)	45.6 (10.72)	45.8 (11.75)	45.6 (11.21)

Gender, Male/Female (Units: participants)

Number
Not Applicable

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID	**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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	127	125	117	129	498 *(calculated)*
Male	47	49	57	45	198 *(calculated)*

Race/Ethnicity, Customized (Units: participants)

Number
Not Applicable

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID	**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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	161	156	157	158	632 *(calculated)*
Black or African American	2	3	1	2	8 *(calculated)*
Asian	0	1	0	1	2 *(calculated)*
Native Hawaiian or other Pacific Islander	0	0	0	0	0 *(calculated)*
American Indian or Alaska Native	0	1	0	0	1 *(calculated)*
Other	11	13	16	13	53 *(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

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID	**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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**
	21.49 (3.587)	20.98 (3.182)	21.50 (3.674)	21.26 (3.614)	21.30 (3.517)

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

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID	**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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**
	24.69 (5.086)	24.67 (5.389)	25.03 (5.137)	24.11 (4.992)	24.62 (5.152)

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.

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID	**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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:	173	174	170	174

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
	-11.6	0.65	-12.2	0.66	-12.2	0.69	-12.7	0.65

Statistical Analysis		
Groups	0.1 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	1.1	
Standard Error of the mean	0.84	
95% Confidence Interval 2-Sided	-0.53 to 2.79	

Statistical Analysis		
Groups	1 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	0.5	
Standard Error of the mean	0.85	
95% Confidence Interval 2-Sided	-1.22 to 2.13	

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	0.5	
Standard Error of the mean	0.88	
95% Confidence Interval 2-Sided	-1.21 to 2.22	

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.

MADRS is 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.

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID	**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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:	173	174	170	174
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
	48.6	51.1	41.2	54.0

Statistical Analysis		
Groups	0.1 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	0.144	
Method	Regression, Logistic	
Odds Ratio (OR)	0.71	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.17	
95% Confidence Interval 2-Sided	0.45 to 1.12	

Statistical Analysis		
Groups	1 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	0.203	
Method	Regression, Logistic	
Odds Ratio (OR)	0.74	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.17	
95% Confidence Interval 2-Sided	0.47 to 1.17	

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	0.005	
Method	Regression, Logistic	
Odds Ratio (OR)	0.52	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.12	
95% Confidence Interval 2-Sided	0.32 to 0.82	

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.

MADRS is 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.

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID	**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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:	173	174	170	174
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
	37.0	35.1	30.0	39.1

Statistical Analysis		
Groups	0.1 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	0.636	
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	0.22	
95% Confidence Interval 2-Sided	0.54 to 1.45	

Statistical Analysis		
Groups	1 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	0.215	
Method	Regression, Logistic	
Odds Ratio (OR)	0.73	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.19	
95% Confidence Interval 2-Sided	0.44 to 1.20	

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	0.034	
Method	Regression, Logistic	
Odds Ratio (OR)	0.58	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	0.35 to 0.96	

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.

MADRS is 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.

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID	**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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:	173	173	166	173
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
	7.5	8.1	9.6	9.2

Statistical Analysis		
Groups	0.1 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	0.711	
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	0.37	
95% Confidence Interval 2-Sided	0.36 to 1.99	

Statistical Analysis

Groups	1 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	0.594	
Method	Regression, Logistic	
Odds Ratio (OR)	0.79	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.34	
95% Confidence Interval 2-Sided	0.34 to 1.85	

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	0.749	
Method	Regression, Logistic	
Odds Ratio (OR)	1.15	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.49	
95% Confidence Interval 2-Sided	0.50 to 2.65	

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.

MADRS is 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.

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID	**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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:	170	171	163	173
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
	14.7	19.3	15.3	23.7

Statistical Analysis		
Groups	0.1 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	0.037	
Method	Regression, Logistic	
Odds Ratio (OR)	0.52	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.16	
95% Confidence Interval 2-Sided	0.28 to 0.96	

Statistical Analysis		
Groups	1 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	0.222	
Method	Regression, Logistic	
Odds Ratio (OR)	0.69	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	0.38 to 1.25	

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	0.042	
Method	Regression, Logistic	
Odds Ratio (OR)	0.52	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.17	
95% Confidence Interval 2-Sided	0.28 to 0.98	

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.

MADRS is 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.

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID	**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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:	170	172	163	173
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
	10.6	10.5	8.0	12.1

Statistical Analysis		
Groups	0.1 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	0.913	
Method	Regression, Logistic	
Odds Ratio (OR)	1.04	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.41	
95% Confidence Interval 2-Sided	0.48 to 2.27	

Statistical Analysis		
Groups	1 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	0.841	
Method	Regression, Logistic	
Odds Ratio (OR)	0.92	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.37	
95% Confidence Interval 2-Sided	0.42 to 2.01	

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	0.239	
Method	Regression, Logistic	
Odds Ratio (OR)	0.61	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.26	
95% Confidence Interval 2-Sided	0.26 to 1.39	

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.

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID		**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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:	165		161		162		170	
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
	-10.07	0.597	-10.21	0.603	-9.07	0.597	-11.16	0.592

Statistical Analysis		
Groups	0.1 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	0.120	
Method	ANCOVA	
Other LS mean	1.10	
Standard Error of the mean	0.705	
95% Confidence Interval 2-Sided	-0.288 to 2.481	

Statistical Analysis		
Groups	1 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	0.184	
Method	ANCOVA	
Other LS mean	0.95	
Standard Error of the mean	0.715	
95% Confidence Interval 2-Sided	-0.452 to 2.354	

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	0.003	
Method	ANCOVA	
Other LS mean	2.09	
Standard Error of the mean	0.711	
95% Confidence Interval 2-Sided	0.692 to 3.484	

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.

	0.1 mg BID TC-5214	**1 mg BID TC-5214**	**4 mg BID TC-5214**	**Placebo**

	Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID		Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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:	173		174		170		174	
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
	-1.5	0.09	-1.6	0.09	-1.7	0.10	-1.7	0.09

Statistical Analysis		
Groups	0.1 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	0.131	
Method	Other MMRM	
Other LS mean	0.2	
Standard Error of the mean	0.12	
95% Confidence Interval	-0.05 to 0.42	

Statistical Analysis		
Groups	1 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	0.12	
95% Confidence Interval 2-Sided	-0.17 to 0.31	

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	0.645	
Method	Other MMRM	
Other LS mean	0.1	
Standard Error of the mean	0.12	
95% Confidence Interval 2-Sided	-0.19 to 0.30	

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.

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor	**1 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, 0.1 mg BID	(SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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:	173	174	170	174
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
	59.5	62.1	58.8	67.8

Statistical Analysis		
Groups	0.1 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	0.046	
Method	Regression, Logistic	
Odds Ratio (OR)	0.62	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	0.38 to 0.99	

Statistical Analysis		
Groups	1 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	0.051	
Method	Regression, Logistic	
Odds Ratio (OR)	0.62	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	0.38 to 1.00	

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	0.040	
Method	Regression, Logistic	
Odds Ratio (OR)	0.60	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	0.37 to 0.98	

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. 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:

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID		**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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:	166		161		161		170	
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
	-8.5	0.58	-8.6	0.59	-8.1	0.58	-9.3	0.58

Statistical Analysis		
Groups	0.1 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	0.273	
Method	ANCOVA	
Other LS mean	0.7	
Standard Error of the mean	0.66	
95% Confidence Interval 2-Sided	-0.58 to 2.03	

Statistical Analysis		
Groups	1 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	0.315	
Method	ANCOVA	
Other LS mean	0.7	
Standard Error of the mean	0.67	
95% Confidence Interval 2-Sided	-0.65 to 2.00	

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	0.078	
Method	ANCOVA	
Other LS mean	1.2	
Standard Error of the mean	0.67	
95% Confidence Interval 2-Sided	-0.13 to 2.51	

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.

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID		**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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:	167		162		164		168	
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
	-3.0	0.42	-3.0	0.43	-2.6	0.42	-3.2	0.42

Statistical Analysis		
Groups	0.1 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	0.590	
Method	Other MMRM	
Other LS mean	0.3	
Standard Error of the mean	0.47	

95% Confidence Interval 2-Sided	-0.68 to 1.19	

Statistical Analysis		
Groups	1 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	0.679	
Method	Other MMRM	
Other LS mean	0.2	
Standard Error of the mean	0.48	
95% Confidence Interval 2-Sided	-0.74 to 1.14	

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	0.215	
Method	Other MMRM	
Other LS mean	0.6	
Standard Error of the mean	0.48	
95% Confidence Interval 2-Sided	-0.35 to 1.53	

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.

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID		**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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:	170		166		157		171	
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
	-4.8	0.50	-5.9	0.50	-5.0	0.51	-6.0	0.50

Statistical Analysis		
Groups	0.1 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	0.052	
Method	Other MMRM	
Other LS mean	1.2	
Standard Error of the mean	0.61	
95% Confidence Interval 2-Sided	-0.01 to 2.38	

Statistical Analysis		
Groups	1 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	0.874	
Method	Other MMRM	
Other LS mean	0.1	
Standard Error of the mean	0.61	
95% Confidence Interval 2-Sided	-1.11 to 1.30	

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	0.099	
Method	Other MMRM	
Other LS mean	1.0	
Standard Error of the mean	0.62	
95% Confidence Interval 2-Sided	-0.19 to 2.24	

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.

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID		**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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:	163		157		144		166	
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
	-8.1	0.55	-8.5	0.56	-7.8	0.57	-8.7	0.55

Statistical Analysis		
Groups	0.1 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	0.394	
Method	Other MMRM	
Other LS mean	0.6	
Standard Error of the mean	0.69	
95% Confidence Interval 2-Sided	-0.77 to 1.95	

Statistical Analysis		
Groups	1 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	0.712	
Method	Other MMRM	
Other LS mean	0.3	
Standard Error of the mean	0.70	
95% Confidence Interval 2-Sided	-1.11 to 1.63	

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	0.167	
Method	Other MMRM	
Other LS mean	1.0	
Standard Error of the mean	0.71	
95% Confidence Interval 2-Sided	-0.41 to 2.38	

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.

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID		**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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:	159		149		131		164	
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
	-9.5	0.59	-10.6	0.60	-9.6	0.62	-11.0	0.59

Statistical Analysis		
Groups	0.1 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	0.046	
Method	Other MMRM	
Other LS mean	1.5	
Standard Error of the mean	0.75	
95% Confidence Interval 2-Sided	0.02 to 2.95	

Statistical Analysis		
Groups	1 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	0.681	
Method	Other MMRM	

Other LS mean	0.3	
Standard Error of the mean	0.75	
95% Confidence Interval 2-Sided	-1.17 to 1.79	

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	0.087	
Method	Other MMRM	
Other LS mean	1.3	
Standard Error of the mean	0.77	
95% Confidence Interval 2-Sided	-0.19 to 2.84	

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.

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID		**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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:	171		168		163		172	
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
	-6.08	0.561	-6.34	0.569	-6.21	0.592	-7.06	0.556

Statistical Analysis		
Groups	0.1 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	0.98	
Standard Error of the mean	0.736	
95% Confidence Interval 2-Sided	-0.464 to 2.427	

Statistical Analysis		
Groups	1 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	0.72	
Standard Error of the mean	0.746	
95% Confidence Interval 2-Sided	-0.740 to 2.188	

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	0.85	
Standard Error of the mean	0.762	
95% Confidence Interval 2-Sided	-0.649 to 2.346	

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.

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID		**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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:	141		140		126		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
	-2.0	0.21	-1.8	0.22	-1.9	0.24	-2.1	0.22

Statistical Analysis		
Groups	0.1 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	0.914	
Method	Other MMRM	
Other LS mean	0.0	
Standard Error of the mean	0.29	
95% Confidence Interval 2-Sided	-0.54 to 0.61	

Statistical Analysis		
Groups	1 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	0.446	
Method	Other MMRM	
Other LS mean	0.2	
Standard Error of the mean	0.30	
95% Confidence Interval 2-Sided	-0.36 to 0.81	

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	0.656	
Method	Other MMRM	
Other LS mean	0.1	
Standard Error of the mean	0.31	
95% Confidence Interval 2-Sided	-0.47 to 0.75	

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.

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID		**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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:	171		168		163		172	
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
	-2.1	0.20	-2.2	0.20	-2.2	0.21	-2.4	0.20

Statistical Analysis		
Groups	0.1 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	0.248	
Method	Other MMRM	
Other LS mean	0.3	
Standard Error of the mean	0.26	
95% Confidence Interval 2-Sided	-0.21 to 0.82	

Statistical Analysis		
Groups	1 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	0.498	
Method	Other MMRM	
Other LS mean	0.2	
Standard Error of the mean	0.27	
95% Confidence Interval 2-Sided	-0.34 to 0.70	

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	0.441	
Method	Other MMRM	
Other LS mean	0.2	
Standard Error of the mean	0.27	
95% Confidence Interval 2-Sided	-0.32 to 0.74	

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.

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID		**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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:	171		168		163		172	
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
	-2.0	0.20	-2.1	0.20	-2.0	0.21	-2.3	0.20

Statistical Analysis		
Groups	0.1 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	0.174	
Method	Other MMRM	
Other LS mean	0.4	
Standard Error of the mean	0.26	
95% Confidence Interval 2-Sided	-0.16 to 0.87	

Statistical Analysis		
Groups	1 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	0.402	
Method	Other MMRM	
Other LS mean	0.2	
Standard Error of the mean	0.27	
95% Confidence Interval 2-Sided	-0.30 to 0.74	

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	0.197	
Method	Other MMRM	
Other LS mean	0.3	
Standard Error of the mean	0.27	
95% Confidence Interval 2-Sided	-0.18 to 0.88	

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 (Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form) 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.

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID		**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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:	171		166		162		172	
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
	13.08	1.388	13.24	1.402	11.84	1.409	14.55	1.391

Statistical Analysis		
Groups	0.1 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	0.371	
Method	ANCOVA	
Other LS mean	-1.47	
Standard Error of the mean	1.643	
95% Confidence Interval 2-Sided	-4.697 to 1.756	

Statistical Analysis		
Groups	1 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	0.432	
Method	ANCOVA	
Other LS mean	-1.32	
Standard Error of the mean	1.672	
95% Confidence Interval 2-Sided	-4.597 to 1.967	

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	0.105	
Method	ANCOVA	
Other LS mean	-2.71	
Standard Error of the mean	1.672	
95% Confidence Interval 2-Sided	-5.992 to 0.573	

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. Higher scores are indicative of greater enjoyment or satisfaction in each domain.

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.

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID		**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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:	153		154		151		157	
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
	0.6	0.08	0.7	0.08	0.5	0.08	0.7	0.08

Statistical Analysis		
Groups	0.1 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	0.312	
Method	ANCOVA	
Other LS mean	-0.1	
Standard Error of the mean	0.10	
95% Confidence Interval 2-Sided	-0.29 to 0.09	

Statistical Analysis		
Groups	1 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	0.885	
Method	ANCOVA	
Other LS mean	0.0	
Standard Error of the mean	0.10	
95% Confidence Interval 2-Sided	-0.18 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	0.067	
Method	ANCOVA	
Other LS mean	-0.2	
Standard Error of the mean	0.10	
95% Confidence Interval 2-Sided	-0.37 to 0.01	

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. Higher scores are indicative of greater enjoyment or satisfaction in each domain.

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.

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID		**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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:	170		166		162		172	
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
	0.7	0.08	0.7	0.08	0.6	0.08	0.8	0.08

Statistical Analysis		
Groups	0.1 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	0.152	
Method	ANCOVA	
Other LS mean	-0.1	
Standard Error of the mean	0.10	
95% Confidence Interval 2-Sided	-0.33 to 0.05	

Statistical Analysis		
Groups	1 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	0.078	
Method	ANCOVA	
Other LS mean	-0.2	
Standard Error of the mean	0.10	
95% Confidence Interval 2-Sided	-0.37 to 0.02	

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	0.033	
Method	ANCOVA	
Other LS mean	-0.2	
Standard Error of the mean	0.10	
95% Confidence Interval 2-Sided	-0.41 to -0.02	

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 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.

	0.1 mg BID TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 0.1 mg BID		**1 mg BID TC-5214** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1 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:	171		168		163		172	
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	0.128	0.0147	0.139	0.0149	0.133	0.0155	0.139	0.0146
EQ-5D VAS score	16.4	1.52	17.0	1.54	15.9	1.61	18.7	1.51

Statistical Analysis		
Groups	0.1 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	0.543	Analysis for change in EQ-5D index score from randomization (Week 8) to end of treatment (Week 16)
Method	Other MMRM	
Other LS mean	-0.011	
Standard Error of the mean	0.0181	
95% Confidence Interval 2-Sided	-0.0465 to 0.0245	

Statistical Analysis		
Groups	1 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	0.998	Analysis for change in EQ-5D index score from randomization (Week 8) to end of treatment (Week 16)
Method	Other MMRM	
Other LS mean	0.000	
Standard Error of the mean	0.0183	
95% Confidence Interval 2-Sided	-0.0360 to 0.0361	

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	0.743	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	0.0188	
95% Confidence Interval 2-Sided	-0.0432 to 0.0308	

Statistical Analysis		
Groups	0.1 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	0.244	Analysis of change in EQ-5D VAS score from randomization (Week 8) to end of treatment (Week 16)
Method	Other MMRM	
Other LS mean	-2.3	
Standard Error of the mean	1.95	
95% Confidence Interval 2-Sided	-6.10 to 1.56	

Statistical Analysis		
Groups	1 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	0.389	Analysis of change in EQ-5D VAS score from randomization (Week 8) to end of treatment (Week 16)
Method	Other MMRM	
Other LS mean	-1.7	
Standard Error of the mean	1.98	
95% Confidence Interval 2-Sided	-5.59 to 2.18	

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	0.165	Analysis of change in EQ-5D VAS score from randomization (Week 8) to end of treatment (Week 16)
Method	Other MMRM	
Other LS mean	-2.8	
Standard Error of the mean	2.02	
95% Confidence Interval 2-Sided	-6.79 to 1.16	

Limitations and Caveats

Adverse Events

View Adverse Events