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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 between 2 September 2010 and 27 September 2011.
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

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	**Total** *(=sum per row)*
Started	147	148	295 *(calculated)*
Received treatment	147	146	293 *(calculated)*
Completed	122	121	243 *(calculated)*
Not Completed: *(=Started - Completed)*	25 *(calculated)*	27 *(calculated)*	52 *(calculated)*
Reason for Not Completed			
Total: *(=sum per column)*	25 *(calculated)*	27 *(calculated)*	52 *(calculated)*
Withdrawal by Subject	5	6	11 *(calculated)*
Other **Eligibility criteria not fulfilled**	0	2	2 *(calculated)*
Adverse Event	12	10	22 *(calculated)*
Other **Severe non-compliance to protocol**	1	2	3 *(calculated)*
Other **Condition under investigation worsened**	2	1	3 *(calculated)*
Lack of Efficacy	2	0	2 *(calculated)*
Other **Study-specific withdrawal criteria**	1	2	3 *(calculated)*
Lost to Follow-up	2	3	5 *(calculated)*
Other **Not specified**	0	1	1 *(calculated)*

Baseline Characteristics

Overall Number of Baseline Participants			
	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 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	147	148	295 *(calculated)*
Baseline Analysis Population Description			

Age Continuous (Units: years) Mean Standard Deviation			
	TC-5214	**Placebo**	**Total**

	Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID	Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
	46.1 (11.25)	43.4 (11.31)	44.8 (11.34)

Gender, Male/Female (Units: participants)

Number
Not Applicable

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	**Total** *(=sum per row)*
Female	94	95	189 *(calculated)*
Male	53	53	106 *(calculated)*

Race/Ethnicity, Customized (Units: participants)

Number
Not Applicable

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	**Total** *(=sum per row)*
White	146	148	294 *(calculated)*
Black or African American	0	0	0 *(calculated)*
Asian	0	0	0 *(calculated)*
Native Hawaiian or other Pacific Islander	0	0	0 *(calculated)*
American Indian or Alaska Native	0	0	0 *(calculated)*
Other	1	0	1 *(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

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	**Total**
	20.0 (2.77)	20.5 (3.41)	20.2 (3.11)

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

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	**Total**
	24.3 (4.92)	25.1 (4.72)	24.7 (4.82)

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.

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	145		145	
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
	-11.7	0.71	-11.6	0.70

Statistical Analysis		
Groups	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	0.944	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	-0.1	
Standard Error of the mean	0.91	
95% Confidence Interval 2-Sided	-1.86 to 1.73	

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.

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID
Number of Participants Analyzed:	145	145
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
	48.3	49.0

Statistical Analysis		
Groups	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	0.974	
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	0.26	
95% Confidence Interval 2-Sided	0.61 to 1.66	

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.

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID
Number of Participants Analyzed:	145	145
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
	33.8	26.9

Statistical Analysis		
Groups	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	0.184	
Method	Regression, Logistic	
Odds Ratio (OR)	1.45	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	0.84 to 2.53	

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.

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID
Number of Participants Analyzed:	144	144
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
	7.6	6.3

Statistical Analysis		
Groups	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	0.461	
Method	Regression, Logistic	
Odds Ratio (OR)	1.44	TC-5214 is the numerator in the OR, OR>1 represents a result in favor of TC-5214.
Standard Error of the mean	0.71	
95% Confidence Interval 2-Sided	0.55 to 3.78	

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.

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID
Number of Participants Analyzed:	138	141
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
	14.5	16.3

Statistical Analysis		
Groups	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	0.689	
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	0.31	
95% Confidence Interval 2-Sided	0.43 to 1.75	

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.

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID
Number of Participants Analyzed:	139	142
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
	7.9	9.2

Statistical Analysis		
Groups	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	0.831	
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	0.44	
95% Confidence Interval 2-Sided	0.35 to 2.32	

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.

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	135		139	
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
	-9.4	0.56	-9.8	0.55

Statistical Analysis		
Groups	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	0.525	
Method	ANCOVA	
Other LS mean	0.5	
Standard Error of the mean	0.72	
95% Confidence Interval 2-Sided	-0.96 to 1.89	

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.

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	145		145	
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
	-1.6	0.11	-1.6	0.11

Statistical Analysis		
Groups	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	0.964	
Method	Other MMRM	
Other LS mean	0.0	
Standard Error of the mean	0.14	
95% Confidence Interval	-0.28 to 0.26	

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.

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID
Number of Participants Analyzed:	145	145
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
	64.8	65.5

Statistical Analysis		
Groups	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	0.783	
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	0.25	
95% Confidence Interval 2-Sided	0.54 to 1.58	

10. 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.

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	145		141	
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
	-3.0	0.47	-3.1	0.46

Statistical Analysis		
Groups	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	0.832	Analysis for change in MADRS total score from randomization to Week 9.
Method	Other MMRM	
Other LS mean	0.1	
Standard Error of the mean	0.51	
95% Confidence Interval 2-Sided	-0.89 to 1.11	

11. 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.

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	143		140	
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
	-4.9	0.56	-5.4	0.56

Statistical Analysis		
Groups	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	0.468	
Method	Other MMRM	
Other LS mean	0.5	
Standard Error of the mean	0.67	
95% Confidence Interval 2-Sided	-0.84 to 1.82	

12. 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.

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID	**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID

Number of Participants Analyzed:	135		133	
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
	-7.2	0.62	-8.2	0.62

Statistical Analysis		
Groups	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	0.187	
Method	Other MMRM	
Other LS mean	1.0	
Standard Error of the mean	0.77	
95% Confidence Interval 2-Sided	-0.49 to 2.52	

13. 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.

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	126		132	
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
	-9.1	0.68	-10.3	0.67

Statistical Analysis		
Groups	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	0.145	
Method	Other MMRM	
Other LS mean	1.3	
Standard Error of the mean	0.86	
95% Confidence Interval 2-Sided	-0.44 to 2.95	

14. 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.

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	138		142	
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
	-5.79	0.548	-5.75	0.536

Statistical Analysis		
Groups	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	0.956	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	-0.04	
Standard Error of the mean	0.766	
95% Confidence Interval 2-Sided	-1.549 to 1.466	

15. 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.

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	115		120	
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
	-2.2	0.25	-1.8	0.24

Statistical Analysis		
Groups	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	0.201	Analysis for change in SDS work/school domain score from randomization (Week 8) to end of treatment (Week 16)
Method	Other MMRM	
Other LS mean	-0.4	
Standard Error of the mean	0.30	
95% Confidence Interval 2-Sided	-0.98 to 0.21	

16. 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.

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	138		142	
Change in functional impairment from randomization (Week 8) to end of treatment (Week 16) as measured by SDS social life domain score	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error

Units: units on a scale				
	-2.0	0.19	-1.9	0.19

Statistical Analysis		
Groups	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	0.756	
Method	Other MMRM	
Other LS mean	-0.1	
Standard Error of the mean	0.27	
95% Confidence Interval 2-Sided	-0.62 to 0.45	

17. 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.

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	138		142	
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
	-1.9	0.20	-2.0	0.19

Statistical Analysis		
Groups	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	0.620	
Method	Other MMRM	
Other LS mean	0.1	
Standard Error of the mean	0.27	
95% Confidence Interval 2-Sided	-0.40 to 0.68	

18. 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 total score

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.

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	137		142	
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-	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error

Short Form (Q-LES-Q-SF) % maximum total score Units: units on a scale				
	11.22	1.246	11.07	1.217

Statistical Analysis		
Groups	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	0.924	
Method	ANCOVA	
Other LS mean	0.15	
Standard Error of the mean	1.592	
95% Confidence Interval 2-Sided	-2.981 to 3.286	

19. 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.

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	131		133	
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
	0.3	0.08	0.4	0.07

Statistical Analysis		
Groups	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	0.345	
Method	ANCOVA	
Other LS mean	-0.1	
Standard Error of the mean	0.10	
95% Confidence Interval 2-Sided	-0.30 to 0.10	

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 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.

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	138		142	
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
	0.7	0.08	0.7	0.08

Statistical Analysis		
Groups	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	0.942	
Method	ANCOVA	
Other LS mean	0.0	
Standard Error of the mean	0.10	
95% Confidence Interval 2-Sided	-0.20 to 0.19	

21. 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.

	TC-5214 Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + TC-5214, 1-4 mg BID		**Placebo** Selective serotonin reuptake inhibitor (SSRI)/Serotonin/norepinephrine reuptake inhibitor (SNRI) + Placebo BID	
Number of Participants Analyzed:	138		142	
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
EQ-5D index score	0.109	0.0154	0.120	0.0150
EQ-5D VAS score	13.6	1.59	14.0	1.54

Statistical Analysis		
Groups	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	0.576	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	0.0198	
95% Confidence Interval 2-Sided	-0.0500 to 0.0279	

Statistical Analysis		
Groups	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	0.842	Analysis of change in EQ-5D VAS score from randomization (Week 8) to end of treatment (Week 16)
Method	Other MMRM	
Other LS mean	-0.4	
Standard Error of the mean	2.11	
95% Confidence Interval 2-Sided	-4.58 to 3.73	

Limitations and Caveats

Adverse Events

View Adverse Events