



Clinical trial results:

A Double-blind, Placebo-controlled, Multicenter Study of Sirukumab as Adjunctive Treatment to a Monoaminergic Antidepressant in Adults with Major Depressive Disorder

Summary

EudraCT number	2014-005206-37
Trial protocol	PL GB
Global end of trial date	22 May 2018

Results information

Result version number	v1 (current)
This version publication date	06 June 2019
First version publication date	06 June 2019

Trial information

Trial identification

Sponsor protocol code	CNT0136MDD2001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02473289
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 Route, New Jersey, United States, 08869
Public contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 May 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	22 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the efficacy of sirukumab as adjunctive treatment to monoaminergic antidepressant therapy where sirukumab (administered as a 50 milligram [mg] subcutaneous [SC] injection at Day 1, Day 28 and Day 56 during the 12 week double-blind treatment period) was compared to adjunctive placebo (placebo) based on the change from baseline to 12 week in the depressive symptoms as measured by the total score on the Hamilton Depression Rating Scale (HDRS-17), in subjects diagnosed with Major Depressive Disorder (MDD) who have had a suboptimal response to the current standard oral antidepressant therapy and had a screening and baseline high sensitivity C-Reactive Protein (hsCRP) greater than or equal to (\geq) 0.300 milligrams per deciliter (mg/dL) (International system of units [SI] 3.00 mg/L).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Safety evaluations included monitoring of adverse events (AEs), clinical laboratory tests (hsCRP), hematology, serum chemistry, lipids, and urinalysis), electrocardiograms (ECGs), vital sign measurements (oral temperature, pulse/heart rate, blood pressure), physical examinations, suicidal risk (closely monitored throughout the study for clinical worsening, suicidality, and/or unusual changes in behavior), suicidal ideation and behavior (assessed via Columbia Suicide Severity Rating Scale [C-SSRS]), allergic reactions, injection-site reactions, hepatobiliary abnormalities and early detection of active tuberculosis (TB) and hepatobiliary abnormalities.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Poland: 40
Country: Number of subjects enrolled	Russian Federation: 95
Country: Number of subjects enrolled	United States: 48
Worldwide total number of subjects	193
EEA total number of subjects	43

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	193
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 193 subjects were randomized to one of the two treatment groups: sirukumab 50 milligram (mg) (94 subjects) or placebo (99 subjects) group, out of which 169 subjects completed the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received placebo subcutaneous (SC) injection on Day 1, Day 28 and Day 56, while continuing their baseline oral monoaminergic antidepressant(s).

Arm type	Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received placebo on Day 1, Day 28 and Day 56, while continuing their baseline oral monoaminergic antidepressant(s).

Arm title	Sirukumab 50 mg
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Arm description:

Subjects received sirukumab 50 milligram (mg) on Day 1, Day 28 and Day 56, while continuing their baseline oral monoaminergic antidepressant(s).

Arm type	Experimental
Investigational medicinal product name	Sirukumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received sirukumab 50 milligram (mg) on Day 1, Day 28 and Day 56, while continuing their baseline oral monoaminergic antidepressant(s).

Number of subjects in period 1	Placebo	Sirukumab 50 mg
Started	99	94
Completed	88	81
Not completed	11	13
Consent withdrawn by subject	6	7
Adverse event, non-fatal	2	3
Treatment unblinded + Adverse event	-	1
Unspecified	2	-
Lost to follow-up	1	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects received placebo subcutaneous (SC) injection on Day 1, Day 28 and Day 56, while continuing their baseline oral monoaminergic antidepressant(s).

Reporting group title	Sirukumab 50 mg
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Reporting group description:

Subjects received sirukumab 50 milligram (mg) on Day 1, Day 28 and Day 56, while continuing their baseline oral monoaminergic antidepressant(s).

Reporting group values	Placebo	Sirukumab 50 mg	Total
Number of subjects	99	94	193
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	99	94	193
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	44.1	45.4	-
standard deviation	± 11.73	± 10.83	-
Title for Gender Units: subjects			
Female	75	74	149
Male	24	20	44

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Subjects received placebo subcutaneous (SC) injection on Day 1, Day 28 and Day 56, while continuing their baseline oral monoaminergic antidepressant(s).	
Reporting group title	Sirukumab 50 mg
Reporting group description: Subjects received sirukumab 50 milligram (mg) on Day 1, Day 28 and Day 56, while continuing their baseline oral monoaminergic antidepressant(s).	

Primary: Change From Baseline in Hamilton Depression Rating Scale (HDRS-17) Total Score at Week 12

End point title	Change From Baseline in Hamilton Depression Rating Scale (HDRS-17) Total Score at Week 12
End point description: HDRS-17 is a clinician-administered rating scale designed to assess severity of symptoms in subjects with depression with score range of 0 to 52. Each of the 17 items is rated by clinician on either 3-point (0 to 2) or 5-point scale (0 to 4). The point scale used a rating of 0 (absent), 1 (doubtful to mild), 2 (mild to moderate), 3 (moderate to severe), and 4 (very severe). A total score (0 to 52) was calculated by adding the scores of all 17 items. For each item as well as the total score, a higher score represents a more severe condition. Modified Intent-to-treat 1 (mITT1) analysis set: all randomized subjects with high sensitivity c-reactive protein (hsCRP) \geq 3.00 milligram per liter (mg/L) at screening and baseline who receive at least 1 dose of study drug and have both baseline and at least one postbaseline HDRS-17 total score in double-blind (DB) treatment period. Here 'N' (number of subjects analyzed) signifies number of subjects who were evaluable for this endpoint.	
End point type	Primary
End point timeframe: Baseline and Week 12	

End point values	Placebo	Sirukumab 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	44		
Units: Units on a scale				
least squares mean (standard error)	-10.6 (\pm 1.43)	-11.4 (\pm 1.52)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Total 44 subjects were included in this statistical analysis. Here 'MMRM' refers to Mixed-effect Model Using Repeated Measures.	
Comparison groups	Sirukumab 50 mg v Placebo

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31 ^[1]
Method	MMRM
Parameter estimate	Difference of Least Square (LS) Means
Point estimate	-0.8
Confidence interval	
level	Other: 75 %
sides	2-sided
lower limit	-2.77
upper limit	1.1
Variability estimate	Standard error of the mean
Dispersion value	1.67

Notes:

[1] - 1-sided

Secondary: Change From Baseline in HDRS-17 Total Score at Weeks 1, 4 and 8

End point title	Change From Baseline in HDRS-17 Total Score at Weeks 1, 4 and 8
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End point description:

The HDRS-17 is a clinician-administered rating scale designed to assess the severity of symptoms in subjects diagnosed with depression with a score range of 0 to 52. Each of the 17 items is rated by the clinician on either a 3-point (0 to 2) or a 5-point scale (0 to 4). The point scale used a rating of 0 (absent), 1 (doubtful to mild), 2 (mild to moderate), 3 (moderate to severe), and 4 (very severe). A total score (0 to 52) was calculated by adding the scores of all 17 items. For each item as well as the total score, a higher score represents a more severe condition. mITT1 analysis set: all randomized participants with hsCRP \geq 3.00 mg/L at screening and baseline who receive at least 1 dose of study drug and have both baseline and at least one postbaseline HDRS-17 total score in DB treatment period. 'n' (number of subjects analyzed)- number of subjects analyzed at each specified timepoint, for each arm.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 1, 4 and 8

End point values	Placebo	Sirukumab 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Units on a scale				
least squares mean (standard error)				
Change at Week 1 (n= 46, 47)	-5.1 (\pm 1.03)	-4.6 (\pm 1.15)		
Change at Week 4 (n= 46, 45)	-7.5 (\pm 1.21)	-7.8 (\pm 1.33)		
Change at Week 8 (n= 42, 45)	-7.9 (\pm 1.29)	-11.0 (\pm 1.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Remission as Assessed by HDRS-17 Total Score at Week 12

End point title	Percentage of Subjects with Remission as Assessed by HDRS-17 Total Score at Week 12
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End point description:

Remission- Percentage of subjects with HDRS-17 total score less than or equal to (\leq) 7 were considered as remitters. HDRS-17 defined as clinician-administered rating scale designed to assess severity of symptoms in subjects diagnosed with depression with score range of 0 to 52. Each of 17 items is rated by clinician on either a 3-point (0 to 2) or a 5-point scale (0 to 4). The point scale used a rating of 0 (absent), 1 (doubtful to mild), 2 (mild to moderate), 3 (moderate to severe), and 4 (very severe). A total score (0 to 52) was calculated by adding scores of all 17 items. For each item as well as total score, a higher score represents a more severe condition. mITT1 analysis set: all randomized subjects with hsCRP \geq 3.00 mg/L at screening and baseline who receive at least 1 dose of study drug and have both baseline and at least one postbaseline HDRS-17 total score in DB treatment period. 'N' (number of subjects analyzed)- number of subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Week 12

End point values	Placebo	Sirukumab 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	44		
Units: Percentage of subjects				
number (not applicable)	19.0	15.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Response as Assessed by HDRS-17 Total Score at Week 12

End point title	Percentage of Subjects with Response as Assessed by HDRS-17 Total Score at Week 12
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End point description:

Response- Percentage of subjects with greater than or equal to (\geq) 50 percent (%) improvement on HDRS-17 total score from baseline at Week 12 were considered as responders. HDRS-17 is clinician-administered rating scale designed to assess severity of symptoms in subjects with depression with score range 0-52. Each of 17 items rated by clinician either 3-point (0-2) or 5-point scale (0-4). Point scale used rating of 0 (absent), 1 (doubtful to mild), 2 (mild to moderate), 3 (moderate to severe), and 4 (very severe). Total score (0-52) was calculated by adding scores of all 17 items. For each item as well as total score, higher score represents more severe condition. mITT1 analysis set: all randomized subjects with hsCRP \geq 3.00 mg/L at screening and baseline who receive at least 1 dose of study drug and have both baseline and at least one postbaseline HDRS-17 total score in DB treatment period. 'N' (number of subjects analyzed)- number of subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Week 12

End point values	Placebo	Sirukumab 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	44		
Units: Percentage of subjects				
number (not applicable)	33.3	34.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Global Impression - Severity (CGI-S) Total Score at Weeks 1, 4, 8, 12, 16, and 22

End point title	Change From Baseline in Clinical Global Impression - Severity (CGI-S) Total Score at Weeks 1, 4, 8, 12, 16, and 22
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End point description:

CGI-S defined as clinician-rated scale that assesses the severity of mental illness on a scale of 0 to 7. Considering total clinical experience, a subject was assessed on severity of mental illness at the time of rating according to: 1: normal, not at all ill; 2: borderline mentally ill; 3: mildly ill; 4: moderately ill; 5: markedly ill; 6: severely ill; 7: among the most extremely ill patients. A higher score implies a more severe condition. mITT1 analysis set: all randomized subjects with hsCRP \geq 3.00 mg/L at screening and baseline who receive at least 1 dose of study drug and have both baseline and at least one postbaseline HDRS-17 total score in DB treatment period. 'n' (number of subjects analyzed)- number of subjects analyzed at each specified timepoint, for each arm.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 1, 4, 8, 12, 16, and 22

End point values	Placebo	Sirukumab 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Units on a scale				
least squares mean (standard error)				
Change at Week 1 (n=46, 47)	-0.6 (\pm 0.14)	-0.7 (\pm 0.15)		
Change at Week 4 (n=46, 45)	-1.1 (\pm 0.16)	-1.0 (\pm 0.17)		
Change at Week 8 (n=42, 45)	-1.4 (\pm 0.18)	-1.5 (\pm 0.19)		
Change at Week 12 (n=44, 44)	-1.5 (\pm 0.21)	-1.9 (\pm 0.22)		
Change at Week 16 (n=42, 44)	-1.9 (\pm 0.23)	-2.1 (\pm 0.24)		
Change at Week 22 (n=42, 43)	-2.0 (\pm 0.24)	-2.3 (\pm 0.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient Health Questionnaire (PHQ-9) Total Score at Weeks 1, 4, 8, 12, 16, and 22

End point title	Change From Baseline in Patient Health Questionnaire (PHQ-9) Total Score at Weeks 1, 4, 8, 12, 16, and 22
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End point description:

The PHQ-9 used as a subject-reported measure of depressive symptomatology. The PHQ-9 is 9-item scale, where each item is rated on a 4-point scale (0=Not at all, 1=Several Days, 2=More than half the days, and 3=Nearly every day). The subject's item responses were summed to provide a total score range of 0 to 27. Higher scores indicates greater severity of depressive symptoms. The recall period is 2 weeks. mITT1 analysis set: all randomized participants with hsCRP \geq 3.00 mg/L at screening and baseline who receive at least 1 dose of study drug and have both baseline and at least one postbaseline HDRS-17 total score in DB treatment period. 'n' (number of subjects analyzed)- number of subjects analyzed at each specified timepoint, for each arm.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 1, 4, 8, 12, 16, and 22

End point values	Placebo	Sirukumab 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Units on a scale				
least squares mean (standard error)				
Change at Week 1 (n= 45, 47)	-2.5 (\pm 0.58)	-3.1 (\pm 0.61)		
Change at Week 4 (n= 45, 45)	-4.4 (\pm 0.75)	-5.3 (\pm 0.79)		
Change at Week 8 (n= 41, 45)	-5.6 (\pm 0.86)	-7.6 (\pm 0.87)		
Change at Week 12 (n= 43, 44)	-7.5 (\pm 0.98)	-8.9 (\pm 1.00)		
Change at Week 16 (n= 42, 44)	-8.2 (\pm 0.98)	-9.6 (\pm 1.00)		
Change at Week 22 (n= 41, 43)	-9.1 (\pm 1.04)	-10.7 (\pm 1.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Snaith Hamilton Pleasure Scale (SHAPS) Total Score (Definition 1) at Weeks 1, 4, 8, 12, 16, and 22

End point title	Change From Baseline in Snaith Hamilton Pleasure Scale (SHAPS) Total Score (Definition 1) at Weeks 1, 4, 8, 12, 16, and 22
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End point description:

The Snaith-Hamilton Pleasure Scale (SHAPS) is short, 14-item instrument to measure anhedonia. Each of the 14 items has a set of four response categories (Definition 1): Definitely Agree (=1), Agree (= 2), Disagree (= 3), and Definitely Disagree (= 4). A SHAPS total score was calculated as the sum of the 14 item scores with a total score range from 14 to 56. A higher total score indicates higher levels of state anhedonia. mITT1 analysis set: all randomized subjects with hsCRP \geq 3.00 mg/L at screening and baseline who receive at least 1 dose of study drug and have both baseline and at least one postbaseline HDRS-17 total score in DB treatment period. 'n' (number of subjects analyzed)- number of subjects analyzed at each specified timepoint, for each arm.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 1, 4, 8, 12, 16, and 22

End point values	Placebo	Sirukumab 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Units on a scale				
least squares mean (standard error)				
Change at Week 1 (n= 45, 47)	-1.4 (± 0.72)	-3.3 (± 0.74)		
Change at Week 4 (n= 45, 45)	-3.9 (± 0.75)	-5.1 (± 0.78)		
Change at Week 8 (n= 41, 45)	-5.8 (± 0.87)	-7.0 (± 0.88)		
Change at Week 12 (n= 43, 44)	-5.9 (± 1.00)	-8.9 (± 1.02)		
Change at Week 16 (n= 42, 44)	-7.0 (± 1.11)	-8.8 (± 1.12)		
Change at Week 22 (n= 41, 43)	-7.8 (± 1.11)	-10.6 (± 1.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Snaith Hamilton Pleasure Scale (SHAPS) Total Score (Definition 2) at Weeks 1, 4, 8, 12, 16, and 22

End point title	Change From Baseline in Snaith Hamilton Pleasure Scale (SHAPS) Total Score (Definition 2) at Weeks 1, 4, 8, 12, 16, and 22
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End point description:

The Snaith–Hamilton Pleasure Scale (SHAPS) is short, 14-item instrument to measure anhedonia. Each of the 14 items has a set of four response categories (Definition 2): Definitely Agree (= 0), Agree (= 0), Disagree (= 1), and Definitely Disagree (= 1). A SHAPS total score was calculated as the sum of the 14 item scores with a score range from 0 to 14. A higher total score indicates higher levels of state anhedonia. mITT1 analysis set: all randomized subjects with hsCRP \geq 3.00 mg/L at screening and baseline who receive at least 1 dose of study drug and have both baseline and at least one postbaseline HDRS-17 total score in DB treatment period. 'n' (number of subjects analyzed)- number of subjects analyzed at each specified timepoint, for each arm.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 1, 4, 8, 12, 16, and 22

End point values	Placebo	Sirukumab 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Units on a scale				
least squares mean (standard error)				
Change at Week 1 (n= 45, 47)	-1.2 (± 0.45)	-2.0 (± 0.47)		
Change at Week 4 (n= 45, 45)	-2.2 (± 0.49)	-3.3 (± 0.51)		
Change at Week 8 (n= 41, 45)	-3.6 (± 0.57)	-4.4 (± 0.57)		
Change at Week 12 (n= 43, 44)	-3.7 (± 0.64)	-5.4 (± 0.66)		
Change at Week 16 (n= 42, 44)	-4.1 (± 0.69)	-5.6 (± 0.70)		

Change at Week 22 (n= 41, 43)	-4.6 (± 0.71)	-6.8 (± 0.72)		
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Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Chronic Illness Therapy (FACIT)- Fatigue Total Score at Weeks 1, 4, 8, 12, 16, and 22

End point title	Change From Baseline in Functional Assessment of Chronic Illness Therapy (FACIT)- Fatigue Total Score at Weeks 1, 4, 8, 12, 16, and 22
End point description:	
<p>The FACIT-Fatigue is a questionnaire that assesses self-reported tiredness, weakness, and difficulty conducting usual activities due to fatigue. The subscale consists 13-item instrument to measure fatigue. Each of the 13 items has a set of five response categories: Not at all (=0), A little bit (=1), Somewhat (=2), Quite a bit (=3) and Very much (=4). A total FACIT-Fatigue subscale score was calculated as the sum of the 13 item scores (reserved scores [4 – score] for all except for 2 items: "I have energy" and "I am able to do my usual activities"), and ranges from 0 to 52, with a higher score indicating less fatigue.</p> <p>mITT1 analysis set: all randomized subjects with hsCRP >= 3.00 mg/L at screening and baseline who receive at least 1 dose of study drug and have both baseline and at least one postbaseline HDRS-17 total score in DB treatment period. 'n' (number of subjects analyzed)- number of subjects analyzed at each specified timepoint, for each arm.</p>	
End point type	Secondary
End point timeframe:	
Baseline and Weeks 1, 4, 8, 12, 16, and 22	

End point values	Placebo	Sirukumab 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change at Week 1 (n= 45, 47)	1.75 (± 4.671)	4.91 (± 10.097)		
Change at Week 4 (n= 45, 45)	6.87 (± 10.119)	6.44 (± 9.633)		
Change at Week 8 (n= 41, 45)	8.93 (± 9.913)	10.09 (± 10.346)		
Change at Week 12 (n= 43, 44)	11.65 (± 13.476)	13.82 (± 11.486)		
Change at Week 16 (n= 42, 44)	13.55 (± 12.029)	13.95 (± 12.066)		
Change at Week 22 (n= 41, 43)	14.54 (± 13.585)	17.23 (± 12.051)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 26 weeks

Adverse event reporting additional description:

The safety analysis set included all randomized subjects who received at least 1 dose of study agent in the double-blind phase.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Sirukumab 50 mg
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Reporting group description:

Subjects received sirukumab 50 milligram (mg) on Day 1, Day 28 and Day 56, while continuing on their baseline oral monoaminergic antidepressant(s).

Reporting group title	Placebo
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Reporting group description:

Subjects received placebo subcutaneous (SC) injection on Day 1, Day 28 and Day 56, while continuing their baseline oral monoaminergic antidepressant(s).

Serious adverse events	Sirukumab 50 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 94 (3.19%)	2 / 99 (2.02%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Transaminases Increased			
subjects affected / exposed	0 / 94 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	1 / 94 (1.06%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression Suicidal			

subjects affected / exposed	1 / 94 (1.06%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide Attempt			
subjects affected / exposed	0 / 94 (0.00%)	1 / 99 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 94 (1.06%)	0 / 99 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Sirukumab 50 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 94 (20.21%)	13 / 99 (13.13%)	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 94 (5.32%)	12 / 99 (12.12%)	
occurrences (all)	5	19	
General disorders and administration site conditions			
Injection Site Erythema			
subjects affected / exposed	11 / 94 (11.70%)	0 / 99 (0.00%)	
occurrences (all)	15	0	
Injection Site Pain			
subjects affected / exposed	5 / 94 (5.32%)	1 / 99 (1.01%)	
occurrences (all)	8	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 May 2015	Amendment INT-2 included following changes: Additional clinical laboratory assessment (neutrophils, platelets, and liver enzymes) at the Week 4 visit were added in response to feedback received from Food and Drug Administration (FDA); Clarification was made that the Structured Interview Guide for the Hamilton Depression Scale (SIGH-D) scale will be used for the Hamilton Depression Rating Scale (HDRS-17) assessment.
03 February 2016	Amendment INT-4 included following changes: List of allowed antidepressants, concomitant therapies and comorbidities in subjects with Major Depressive Disorder (MDD) was updated to include subjects who may be more reflective of the general population of subjects with MDD; Screening assessments of the first screening visit were divided over 2 days to stage the screening assessments in order of priority and allow more flexibility to the sites and the study subjects. However, it was clarified that Columbia Suicide Severity Rating Scale (C-SSRS), Inventory of Depressive Symptomatology-Clinician Rated 30 Item Scale (IDS-C30) total score and HDRS17 were to be performed on the same day; Acceptable improvement on HDRS17 total score from the screening to baseline visit was increased from less than (<) 20 percent (%) to less than or equal to (= <) 25% to reflect the most commonly used criteria for minimal response; Orthostatic vital sign evaluation was removed as study agent has no effect on blood pressure; Inclusion criteria, exclusion criteria and prestudy and concomitant therapy criteria were updated to have a better reflection of the general population of subjects with MDD. To achieve better understanding of the relationship between C-reactive protein (CRP) (and potentially other inflammatory biomarkers) and clinical response, additional 50 subjects with screening hsCRP levels <0.300 mg/dL and a 4th stratum of hsCRP level 0.000 to <0.300 milligrams per deciliter (mg/dL) (International system of units [SI] 3.00 mg/L) were added. Related secondary objectives were also added and analyses were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported