Clinical trial results:
Phase II, multicenter, randomized, double-blind, two-part, placebo-controlled, parallel-group, study to assess the effects of ralmitaront in participants with schizophrenia or schizoaffective disorder and negative symptoms

Summary

EudraCT number	2020-004752-16
Trial protocol	ES PL BG HR
Global end of trial date	12 March 2023

Results information

Result version number	v1 (current)
This version publication date	24 March 2024
First version publication date	24 March 2024

Trial information

Trial identification

Sponsor protocol code	BP40283

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, 4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche, +41 616878333, global.trial_information@roche.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	13 July 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 March 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to compare the effectiveness of placebo to ralmitaront as monotherapy or as add-on therapy on negative symptoms in participants with schizophrenia or schizoaffective disorder.

Protection of trial subjects:

All participants were required to sign an Informed Consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 October 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 86
Country: Number of subjects enrolled	Ukraine: 24
Country: Number of subjects enrolled	Japan: 16
Country: Number of subjects enrolled	Spain: 5
Worldwide total number of subjects	131
EEA total number of subjects	5

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)	131
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Male or female participants aged 18-55 years (inclusive) with a diagnosis of schizophrenia or schizoaffective disorder.

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	Part A: Monotherapy (placebo)

Arm description:

Participants received placebo each day (QD) for 12 weeks after a 1-week washout from their usual antipsychotic therapy.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

3 capsules taken orally each day (QD)

Arm title	Part A: Monotherapy (150 mg)

Arm description:

Participants received 150 mg of ralmitaront QD for 12 weeks after a 1-week washout from their usual antipsychotic therapy.

Arm type	Experimental
Investigational medicinal product name	Ralmitaront
Investigational medicinal product code	
Other name	RO6889450
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

3 capsules taken orally QD

Arm title	Part B: Add-on Therapy (placebo)

Arm description:

Participants received placebo QD for 12 weeks in addition to their usual antipsychotic therapy.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

3 capsules taken orally each day (QD) in addition to usual prescribed antipsychotic therapy (prior to protocol v5); 6 capsules taken orally each day (QD) in addition to usual prescribed antipsychotic therapy (after protocol v5)

Arm title	Part B: Add-on Therapy (45 mg)

Arm description:

Participants received 45 mg of ralmitaront QD 12 weeks in addition to their usual antipsychotic therapy (prior to protocol v5; arm was removed thereafter).

Arm type	Experimental
Investigational medicinal product name	Ralmitaront
Investigational medicinal product code	
Other name	RO6889450
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

3 capsules taken orally each day (QD) in addition to usual prescribed antipsychotic therapy (prior to protocol v5; removed thereafter)

Arm title	Part B: Add-on Therapy (150 mg)

Arm description:

Participants received 150 mg of ralmitaront QD 12 weeks in addition to their usual antipsychotic therapy.

Arm type	Experimental
Investigational medicinal product name	Ralmitaront
Investigational medicinal product code	
Other name	RO6889450
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

3 capsules taken orally each day (QD) in addition to usual prescribed antipsychotic therapy (prior to protocol v5); 6 capsules taken orally each day (QD) in addition to usual prescribed antipsychotic therapy (after protocol v5)

Arm title	Part B: Add-on Therapy (300 mg)

Arm description:

Participants received 300 mg of ralmitaront QD 12 weeks in addition to their usual antipsychotic therapy (after protocol v5).

Arm type	Experimental
Investigational medicinal product name	Ralmitaront
Investigational medicinal product code	
Other name	RO6889450
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

6 capsules taken orally each day (QD) in addition to usual prescribed antipsychotic therapy (after protocol v5)

Number of subjects in period 1	Part A: Monotherapy (placebo)	Part A: Monotherapy (150 mg)	Part B: Add-on Therapy (placebo)
Started	15	12	37
Completed	10	7	33
Not completed	5	5	4
Consent withdrawn by subject	1	2	1
Physician decision	-	2	-
Adverse event, non-fatal	2	1	-
Death	-	-	1
Disease relapse	1	-	-
Study terminated by sponsor	-	-	-
Lost to follow-up	-	-	2
Protocol deviation	1	-	-

Number of subjects in period 1	Part B: Add-on Therapy (45 mg)	Part B: Add-on Therapy (150 mg)	Part B: Add-on Therapy (300 mg)
Started	5	30	32
Completed	5	27	29
Not completed	0	3	3
Consent withdrawn by subject	-	1	3
Physician decision	-	-	-
Adverse event, non-fatal	-	1	-
Death	-	-	-
Disease relapse	-	-	-
Study terminated by sponsor	-	1	-
Lost to follow-up	-	-	-
Protocol deviation	-	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Part A: Monotherapy (placebo)
Reporting group description:	
Participants received placebo each day (QD) for 12 weeks after a 1-week washout from their usual antipsychotic therapy.	
Reporting group title	Part A: Monotherapy (150 mg)
Reporting group description:	
Participants received 150 mg of ralmitaront QD for 12 weeks after a 1-week washout from their usual antipsychotic therapy.	
Reporting group title	Part B: Add-on Therapy (placebo)
Reporting group description:	
Participants received placebo QD for 12 weeks in addition to their usual antipsychotic therapy.	
Reporting group title	Part B: Add-on Therapy (45 mg)
Reporting group description:	
Participants received 45 mg of ralmitaront QD 12 weeks in addition to their usual antipsychotic therapy (prior to protocol v5; arm was removed thereafter).	
Reporting group title	Part B: Add-on Therapy (150 mg)
Reporting group description:	
Participants received 150 mg of ralmitaront QD 12 weeks in addition to their usual antipsychotic therapy.	
Reporting group title	Part B: Add-on Therapy (300 mg)
Reporting group description:	
Participants received 300 mg of ralmitaront QD 12 weeks in addition to their usual antipsychotic therapy (after protocol v5).	

Reporting group values	Part A: Monotherapy (placebo)	Part A: Monotherapy (150 mg)	Part B: Add-on Therapy (placebo)
Number of subjects	15	12	37
Age categorical Units: Subjects			
Adults (18-64 years)	15	12	37
Age Continuous Units: Years			
arithmetic mean	42.7	43.3	41.3
standard deviation	± 9.9	± 6.6	± 9.7
Sex: Female, Male Units: Participants			
Female	3	3	10
Male	12	9	27
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	0	2
Not Hispanic or Latino	14	11	35
Unknown or Not Reported	0	1	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	8

Native Hawaiian or Other Pacific Islander	0	0	1
Black or African American	12	9	11
White	2	3	16
More than one race	0	0	0
Unknown or Not Reported	0	0	1

Reporting group values	Part B: Add-on Therapy (45 mg)	Part B: Add-on Therapy (150 mg)	Part B: Add-on Therapy (300 mg)
Number of subjects	5	30	32
Age categorical Units: Subjects			
Adults (18-64 years)	5	30	32
Age Continuous Units: Years			
arithmetic mean	41.6	40.0	40.9
standard deviation	± 11.3	± 9.6	± 9.2
Sex: Female, Male Units: Participants			
Female	0	11	12
Male	5	19	20
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	6	5
Not Hispanic or Latino	5	24	27
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	6	4
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	5	7	10
White	0	16	18
More than one race	0	1	0
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	131		
Age categorical Units: Subjects			
Adults (18-64 years)	131		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	39		
Male	92		

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	14		
Not Hispanic or Latino	116		
Unknown or Not Reported	1		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	19		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	54		
White	55		
More than one race	1		
Unknown or Not Reported	1		

End points

End points reporting groups

Reporting group title	Part A: Monotherapy (placebo)
Reporting group description:	
Participants received placebo each day (QD) for 12 weeks after a 1-week washout from their usual antipsychotic therapy.	
Reporting group title	Part A: Monotherapy (150 mg)
Reporting group description:	
Participants received 150 mg of ralmitaront QD for 12 weeks after a 1-week washout from their usual antipsychotic therapy.	
Reporting group title	Part B: Add-on Therapy (placebo)
Reporting group description:	
Participants received placebo QD for 12 weeks in addition to their usual antipsychotic therapy.	
Reporting group title	Part B: Add-on Therapy (45 mg)
Reporting group description:	
Participants received 45 mg of ralmitaront QD 12 weeks in addition to their usual antipsychotic therapy (prior to protocol v5; arm was removed thereafter).	
Reporting group title	Part B: Add-on Therapy (150 mg)
Reporting group description:	
Participants received 150 mg of ralmitaront QD 12 weeks in addition to their usual antipsychotic therapy.	
Reporting group title	Part B: Add-on Therapy (300 mg)
Reporting group description:	
Participants received 300 mg of ralmitaront QD 12 weeks in addition to their usual antipsychotic therapy (after protocol v5).	

Primary: Brief Negative Symptoms Scale (BNSS) Avolition/Apathy Subscore and Total Score at Baseline and Week 12

End point title	Brief Negative Symptoms Scale (BNSS) Avolition/Apathy Subscore and Total Score at Baseline and Week 12[1]
End point description:	
The BNSS is a 13-item instrument designed for clinical trials that measures the severity of negative symptoms in five domains (subscales): blunted affect, alogia, asociality, anhedonia, and avolition/apathy. Items are rated on a 7-point scale where higher scores indicate worse outcomes, with 0 = absent symptoms and 6 = severe symptoms.	
End point type	Primary
End point timeframe:	
Baseline to Week 12	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical analysis was planned for this endpoint.

End point values	Part A: Monotherapy (placebo)	Part A: Monotherapy (150 mg)	Part B: Add-on Therapy (placebo)	Part B: Add-on Therapy (45 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14[2]	12[3]	36[4]	5[5]
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline Avolition/Apathy Subscore	5.71 (± 2.81)	5.50 (± 2.71)	6.0 (± 2.3)	6.2 (± 1.3)

Week 12 (Day 84) Avolition/Apathy Subscore	5.50 (± 2.55)	4.67 (± 3.27)	5.0 (± 1.9)	5.3 (± 1.0)

Notes:

[2] - Week 12 n = 10

[3] - Week 12 n = 6

[4] - Week 12 n = 31

[5] - Week 12 n = 4

End point values	Part B: Add-on Therapy (150 mg)	Part B: Add-on Therapy (300 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[6]	32[7]		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline Avolition/Apathy Subscore	5.8 (± 1.9)	5.9 (± 2.4)		
Week 12 (Day 84) Avolition/Apathy Subscore	4.1 (± 2.1)	4.7 (± 2.1)		

Notes:

[6] - Week 12 n = 20

[7] - Week 12 n = 21

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression Severity (CGI-S) Overall Scores

End point title	Clinical Global Impression Severity (CGI-S) Overall Scores[8]

End point description:

The CGI-S measures the severity of illness on a 7-point scale ranging from no symptoms to very severe symptoms, with higher scores indicating greater severity.

End point type	Secondary

End point timeframe:

Baseline to week 12

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was specific to study part B.

End point values	Part B: Add-on Therapy (placebo)	Part B: Add-on Therapy (45 mg)	Part B: Add-on Therapy (150 mg)	Part B: Add-on Therapy (300 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37[9]	5[10]	30[11]	32[12]
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	4.1 (± 0.7)	3.8 (± 0.4)	3.9 (± 0.7)	4.0 (± 0.7)
Day 14	4.0 (± 0.6)	3.8 (± 0.5)	3.8 (± 0.6)	4.0 (± 0.8)
Day 28	3.9 (± 0.8)	3.8 (± 0.5)	3.8 (± 0.6)	3.7 (± 0.7)
Day 42	3.8 (± 0.8)	3.8 (± 0.5)	3.6 (± 0.6)	3.6 (± 0.7)
Day 56	3.8 (± 0.8)	3.8 (± 0.5)	3.5 (± 0.7)	3.5 (± 0.8)
Day 84	3.7 (± 0.8)	3.8 (± 0.5)	3.4 (± 0.6)	3.5 (± 0.7)

Notes:

[9] - Day 14 n = 35
Day 28 n =34
Day 42 n = 32
Day 56 n = 33
Day 84 n = 31
[10] - Day 14-84 n = 4

[11] - Day 14 n = 27
Day 28 n = 26
Day 42 n = 24
Day 56 n = 24
Day 84 n = 20
[12] - Day 14 n = 31
Day 28 n = 29
Day 42 n = 26
Day 56 n = 25
Day 84 n = 22

Statistical analyses

No statistical analyses for this end point

Secondary: CGI-S Negative Symptoms Scores

End point title	CGI-S Negative Symptoms Scores[13]

End point description:

The CGI-S measures the severity of illness on a 7-point scale ranging from no symptoms to very severe symptoms, with higher scores indicating greater severity.

End point type	Secondary

End point timeframe:

Baseline to week 12

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was specific to study part B.

End point values	Part B: Add-on Therapy (placebo)	Part B: Add-on Therapy (45 mg)	Part B: Add-on Therapy (150 mg)	Part B: Add-on Therapy (300 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37[14]	5[15]	30[16]	32[17]
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	4.4 (± 0.6)	4.2 (± 0.4)	4.3 (± 0.7)	4.3 (± 0.7)
Day 14	4.3 (± 0.7)	4.3 (± 0.5)	3.9 (± 0.7)	4.1 (± 0.7)
Day 28	4.1 (± 0.8)	4.3 (± 0.5)	3.8 (± 0.7)	3.9 (± 0.7)
Day 42	3.9 (± 0.9)	4.0 (± 0.0)	3.8 (± 0.7)	3.7 (± 0.7)
Day 56	3.9 (± 0.8)	4.0 (± 0.0)	3.6 (± 0.7)	3.5 (± 0.7)
Day 84	3.9 (± 0.8)	3.8 (± 0.5)	3.4 (± 0.6)	3.5 (± 0.9)

Notes:

[14] - Day 14 n = 35
Day 28 n = 34
Day 42 n = 32
Day 56 n = 33
Day 84 n = 31
[15] - Day 14-84 n = 4

[16] - Day 14 n = 27
Day 28 n = 26

Day 42 n = 24
Day 56 n = 24
Day 84 n = 20
[17] - Day 14 n = 31
Day 28 n = 29
Day 42 n = 26
Day 56 n = 25
Day 84 n = 22

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression - Improvement (CGI-I) Overall Scores

End point title	Clinical Global Impression - Improvement (CGI-I) Overall Scores

End point description:

The CGI-I assesses clinical change in symptoms as compared to baseline using a 7-point scale ranging from very much improved to very much worse, with higher scores indicating increasing worsening of symptoms.

999 = Value could not be calculated from a single data point.
9999 = Data was not collected for Part B at this timepoint.

End point type	Secondary

End point timeframe:

Up to Week 12 (Day 84)

End point values	Part A: Monotherapy (placebo)	Part A: Monotherapy (150 mg)	Part B: Add-on Therapy (placebo)	Part B: Add-on Therapy (45 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[18]	12[19]	37[20]	5[21]
Units: Units on a scale				
arithmetic mean (standard deviation)				
Day 14	3.71 (± 0.91)	3.56 (± 0.53)	3.7 (± 0.4)	4.0 (± 0.0)
Day 21	4.00 (± 999)	2.00 (± 999)	9999 (± 9999)	9999 (± 9999)
Day 28	3.56 (± 0.73)	3.50 (± 0.76)	3.5 (± 0.7)	4.0 (± 0.0)
Day 35	3.50 (± 0.71)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)
Day 42	3.73 (± 0.65)	3.29 (± 0.76)	3.4 (± 0.7)	3.8 (± 0.5)
Day 56	3.70 (± 0.48)	3.14 (± 0.69)	3.4 (± 0.7)	3.8 (± 0.5)
Day 70	3.50 (± 0.71)	2.86 (± 0.90)	9999 (± 9999)	9999 (± 9999)
Day 84	3.80 (± 0.42)	3.00 (± 0.63)	3.2 (± 0.7)	3.8 (± 0.5)

Notes:

[18] - Day 14 n = 14
Day 21 n = 1
Day 28 n = 9
Day 35 n = 2
Day 42 n = 11
Day 56-84 n = 10
[19] - Day 14 n = 9
Day 21 n = 1
Day 28 n = 8
Day 42 - 70 n = 7
Day 84 n = 6
[20] - Day 14 n = 35
Day 28 n = 34

Day 42 n = 32
Day 56 n = 33
Day 84 n = 31
[21] - Day 14-84 n = 4

End point values	Part B: Add-on Therapy (150 mg)	Part B: Add-on Therapy (300 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[22]	32[23]		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Day 14	3.6 (± 0.5)	3.6 (± 0.6)		
Day 21	9999 (± 9999)	9999 (± 9999)		
Day 28	3.5 (± 0.8)	3.4 (± 0.8)		
Day 35	9999 (± 9999)	9999 (± 9999)		
Day 42	3.3 (± 0.8)	3.3 (± 0.9)		
Day 56	3.4 (± 0.9)	3.1 (± 1.0)		
Day 70	9999 (± 9999)	9999 (± 9999)		
Day 84	3.0 (± 0.9)	3.0 (± 1.0)		

Notes:
[22] - Day 14 n = 27
Day 28 n = 26
Day 42 n = 24
Day 56 n = 24
Day 84 n = 20
[23] - Day 14 n = 31
Day 28 n = 29
Day 42 n = 26
Day 56 n = 25
Day 84 n = 22

Statistical analyses

No statistical analyses for this end point

Secondary: CGI-I Negative Symptoms Scores

End point title	CGI-I Negative Symptoms Scores

End point description:

The CGI-I assesses clinical change in symptoms as compared to baseline using a 7-point scale ranging from very much improved to very much worse, with higher scores indicating increasing worsening of symptoms. Data for this endpoint was not collected for Part B Days 21, 35, and 70.

999 = Value could not be calculated from a single data point.
9999 = Data was not collected at this timepoint.

End point type	Secondary

End point timeframe:

Up to Week 12 (Day 84)

End point values	Part A: Monotherapy (placebo)	Part A: Monotherapy (150 mg)	Part B: Add-on Therapy (placebo)	Part B: Add-on Therapy (45 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[24]	12[25]	37[26]	5[27]
Units: Units on a scale				
arithmetic mean (standard deviation)				
Day 14	3.71 (± 0.61)	3.44 (± 0.73)	3.7 (± 0.5)	4.0 (± 0.0)
Day 21	5.00 (± 999)	4.00 (± 999)	9999 (± 9999)	9999 (± 9999)
Day 28	3.44 (± 0.73)	3.38 (± 0.74)	3.5 (± 0.7)	4.0 (± 0.0)
Day 35	4.50 (± 0.71)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)
Day 42	3.45 (± 0.69)	3.43 (± 0.79)	3.3 (± 0.6)	3.5 (± 0.6)
Day 56	3.50 (± 0.71)	3.43 (± 0.53)	3.2 (± 0.7)	3.5 (± 0.6)
Day 70	3.40 (± 0.70)	3.00 (± 0.82)	9999 (± 9999)	9999 (± 9999)
Day 84	3.10 (± 0.74)	2.83 (± 0.41)	3.1 (± 0.7)	3.0 (± 0.8)

Notes:

[24] - Day 14 n = 14
Day 21 n = 1
Day 28 n = 9
Day 35 n = 2
Day 42 n = 11
Day 56-84 n = 10
[25] - Day 14 n = 9
Day 21 n = 1
Day 28 n = 8
Day 42-70 n = 7
Day 84 n = 6
[26] - Day 14 n = 35
Day 28 n = 34
Day 42 n = 32
Day 56 n = 33
Day 84 n = 31
[27] - Day 14-84 n = 4

End point values	Part B: Add-on Therapy (150 mg)	Part B: Add-on Therapy (300 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[28]	32[29]		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Day 14	3.5 (± 0.6)	3.5 (± 0.6)		
Day 21	9999 (± 9999)	9999 (± 9999)		
Day 28	3.3 (± 0.7)	3.2 (± 0.8)		
Day 35	9999 (± 9999)	9999 (± 9999)		
Day 42	3.3 (± 0.8)	3.2 (± 0.8)		
Day 56	3.2 (± 0.8)	2.9 (± 0.8)		
Day 70	9999 (± 9999)	9999 (± 9999)		
Day 84	2.9 (± 0.9)	2.8 (± 0.9)		

Notes:

[28] - Day 14 n = 27
Day 28 n = 26
Day 42 n = 24
Day 56 n = 24
Day 84 n = 20
[29] - Day 14 n =
Day 28 n = 29
Day 42 n = 26

Day 56 n = 25
Day 84 n = 22

Statistical analyses

No statistical analyses for this end point

Secondary: Positive and Negative Syndrome Scale (PANSS) Total Scores

End point title	Positive and Negative Syndrome Scale (PANSS) Total Scores

End point description:

The PANSS is a 30-item scale for assessing symptoms in participants with schizophrenia. Each item is rated on a 7-point scale where 1 = absent symptoms and 7 = extreme psychopathology. The PANSS Marder factor negative symptom score is calculated from 7 PANSS items while the PANSS Marder factor positive symptom score is calculated from 8 PANSS items, with higher score in both scales indicating greater symptom severity.

9999 = Data was not collected for Part B at this timepoint.

End point type	Secondary

End point timeframe:

Baseline to week 12

End point values	Part A: Monotherapy (placebo)	Part A: Monotherapy (150 mg)	Part B: Add-on Therapy (placebo)	Part B: Add-on Therapy (45 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14[30]	12[31]	37[32]	5[33]
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	67.43 (± 9.35)	67.92 (± 10.86)	71.4 (± 10.3)	62.8 (± 6.7)
Day 14	68.38 (± 10.37)	69.00 (± 11.40)	67.3 (± 8.5)	69.5 (± 13.5)
Day 28	66.10 (± 10.38)	65.44 (± 7.30)	67.0 (± 10.9)	81.3 (± 4.7)
Day 42	70.09 (± 10.88)	65.88 (± 12.01)	68.3 (± 12.7)	73.3 (± 9.8)
Day 56	66.60 (± 8.13)	61.14 (± 6.91)	64.3 (± 11.7)	70.0 (± 7.1)
Day 70	68.50 (± 7.65)	59.57 (± 7.14)	9999 (± 9999)	9999 (± 9999)
Day 84 (Week 12)	64.70 (± 13.92)	59.17 (± 6.27)	64.4 (± 12.2)	74.8 (± 7.2)

Notes:

[30] - Day 14 n = 13
Day 28 n = 10
Day 42 n = 11
Day 56 n = 10
Day 70 n = 10
Day 84 n = 10
[31] - Day 14 n = 10
Day 28 n = 9
Day 42 n = 8
Day 56 n = 7

Day 70 n = 7
Day 84 n = 6
[32] - Day 14 n = 36
Day 28 n = 33
Day 42 n = 32
Day 56 n = 32
Day 84 n = 31
[33] - Day 14 n = 4
Day 28 n = 3
Day 42 n = 4
Day 56 n = 4
Day 84 n = 4

End point values	Part B: Add-on Therapy (150 mg)	Part B: Add-on Therapy (300 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[34]	32[35]		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	69.6 (± 11.1)	67.8 (± 11.1)		
Day 14	67.4 (± 10.5)	67.9 (± 13.6)		
Day 28	66.8 (± 11.4)	66.5 (± 11.1)		
Day 42	61.8 (± 10.9)	64.1 (± 12.5)		
Day 56	63.2 (± 14.4)	61.4 (± 11.7)		
Day 70	9999 (± 9999)	9999 (± 9999)		
Day 84 (Week 12)	59.0 (± 11.1)	60.9 (± 11.3)		

Notes:
[34] - Day 14 n = 26
Day 28 n = 26
Day 42 n = 24
Day 56 n = 24
Day 84 n = 20
[35] - Day 14 n = 30
Day 28 n = 28
Day 42 n = 24
Day 56 n = 23
Day 84 n = 21

Statistical analyses

No statistical analyses for this end point

Secondary: PANSS Symptom Factor Scores

End point title	PANSS Symptom Factor Scores

End point description:

The PANSS is a 30-item scale for assessing symptoms in participants with schizophrenia. Each item is rated on a 7-point scale where 1 = absent symptoms and 7 = extreme psychopathology. The PANSS Marder factor negative symptom score is calculated from 7 PANSS items while the PANSS Marder factor positive symptom score is calculated from 8 PANSS items, with higher score in both scales indicating greater symptom severity.

9999 = Data was not collected for Part B at this timepoint.

End point type	Secondary

End point timeframe:

Baseline to week 12

End point values	Part A: Monotherapy (placebo)	Part A: Monotherapy (150 mg)	Part B: Add-on Therapy (placebo)	Part B: Add-on Therapy (45 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14[36]	12[37]	37[38]	5[39]
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline - Negative symptoms	21.29 (± 4.45)	21.00 (± 5.20)	23.0 (± 4.7)	20.6 (± 3.3)
Day 14 - Negative symptoms	22.46 (± 5.13)	20.40 (± 3.95)	22.9 (± 3.4)	20.8 (± 2.9)
Day 28 - Negative symptoms	18.40 (± 6.67)	20.44 (± 3.68)	20.9 (± 4.8)	20.3 (± 3.1)
Day 42 - Negative symptoms	21.09 (± 5.45)	19.00 (± 5.50)	21.3 (± 4.5)	22.3 (± 3.2)
Day 56 - Negative symptoms	21.10 (± 5.93)	18.71 (± 4.72)	20.4 (± 4.7)	21.8 (± 4.2)
Day 70 - Negative symptoms	21.20 (± 5.07)	17.71 (± 2.75)	9999 (± 9999)	9999 (± 9999)
Day 84 (Week 12) - Negative symptoms	18.90 (± 5.38)	15.33 (± 3.08)	20.5 (± 5.9)	22.5 (± 4.8)
Baseline - Positive symptoms	17.93 (± 3.99)	19.75 (± 3.93)	18.9 (± 4.6)	18.0 (± 3.7)
Day 14 - Positive symptoms	18.23 (± 4.75)	21.30 (± 4.35)	17.8 (± 3.8)	18.3 (± 5.3)
Day 28 - Positive symptoms	17.60 (± 4.77)	19.22 (± 5.19)	17.9 (± 4.3)	24.3 (± 6.0)
Day 42 - Positive symptoms	17.82 (± 4.31)	18.75 (± 4.13)	18.2 (± 4.8)	22.5 (± 6.0)
Day 56 - Positive symptoms	17.90 (± 4.93)	20.71 (± 1.50)	17.7 (± 5.0)	20.5 (± 3.1)
Day 70 - Positive symptoms	19.20 (± 2.86)	19.29 (± 2.69)	9999 (± 9999)	9999 (± 9999)
Day 84 (Week 12) - Positive symptoms	17.70 (± 5.25)	19.67 (± 3.61)	17.3 (± 4.5)	21.5 (± 2.6)

Notes:

[36] - Day 14 n = 13
Day 28 n = 10
Day 42 n = 11
Day 56 n = 10
Day 70 n = 10
Day 84 n = 10

[37] - Day 14 n = 10
Day 28 n = 9
Day 42 n = 8
Day 56 n = 7
Day 70 n = 7
Day 84 n = 6

[38] - Day 14 n = 36
Day 28 n = 33
Day 42 n = 32
Day 56 n = 32
Day 84 n = 31

[39] - Day 14 n = 4
Day 28 n = 3
Day 42 n = 4
Day 56 n = 4
Day 84 n = 4

End point values	Part B: Add-on Therapy (150 mg)	Part B: Add-on Therapy (300 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[40]	32[41]		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline - Negative symptoms	23.3 (± 4.7)	23.5 (± 4.1)		
Day 14 - Negative symptoms	21.8 (± 4.5)	22.2 (± 5.3)		
Day 28 - Negative symptoms	21.5 (± 4.0)	22.1 (± 4.9)		
Day 42 - Negative symptoms	21.5 (± 5.1)	20.7 (± 5.1)		
Day 56 - Negative symptoms	19.8 (± 4.9)	20.3 (± 5.7)		
Day 70 - Negative symptoms	9999 (± 9999)	9999 (± 9999)		
Day 84 (Week 12) - Negative symptoms	18.6 (± 4.4)	19.4 (± 4.8)		

Baseline - Positive symptoms	17.6 (± 4.2)	17.2 (± 5.4)		
Day 14 - Positive symptoms	18.1 (± 3.9)	18.0 (± 5.7)		
Day 28 - Positive symptoms	18.0 (± 4.9)	17.4 (± 5.9)		
Day 42 - Positive symptoms	16.0 (± 4.4)	16.2 (± 4.7)		
Day 56 - Positive symptoms	17.2 (± 6.1)	15.8 (± 4.5)		
Day 70 - Positive symptoms	9999 (± 9999)	9999 (± 9999)		
Day 84 (Week 12) - Positive symptoms	16.5 (± 4.7)	15.5 (± 4.3)		

Notes:

[40] - Day 14 n = 26
Day 28 n = 26
Day 42 n = 24
Day 56 n = 24
Day 84 n = 20
[41] - Day 14 n = 30
Day 28 n = 28
Day 42 n = 24
Day 56 n = 23
Day 84 n = 21

Statistical analyses

No statistical analyses for this end point

Secondary: Brief Negative Symptom Scale (BNSS) Total Scores

End point title	Brief Negative Symptom Scale (BNSS) Total Scores

End point description:

The BNSS is a 13-item instrument designed for clinical trials that measures the severity of negative symptoms in five domains (subscales): blunted affect, alogia, asociality, anhedonia, and avolition/apathy. Items are rated on a 7-point scale (total score range = 0-78) where higher scores indicate worse outcomes, with 0 = absent symptoms and 6 = severe symptoms.

9999 = Data was not collected for Part B at this timepoint.

End point type	Secondary

End point timeframe:

Baseline to week 12

End point values	Part A: Monotherapy (placebo)	Part A: Monotherapy (150 mg)	Part B: Add-on Therapy (placebo)	Part B: Add-on Therapy (45 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14[42]	12[43]	36[44]	5[45]
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	34.79 (± 14.98)	35.17 (± 13.68)	36.6 (± 14.9)	36.4 (± 6.7)
Day 14	35.08 (± 12.48)	32.90 (± 13.47)	36.1 (± 11.4)	29.3 (± 11.1)
Day 28	29.90 (± 14.49)	33.25 (± 8.94)	32.6 (± 12.9)	32.7 (± 7.4)
Day 42	34.09 (± 11.95)	36.38 (± 14.79)	35.1 (± 11.3)	35.0 (± 11.8)
Day 56	37.40 (± 18.60)	34.00 (± 12.12)	30.3 (± 12.1)	37.5 (± 16.3)
Day 70	33.10 (± 7.23)	34.00 (± 15.15)	9999 (± 9999)	9999 (± 9999)

Day 84 (Week 12)	30.40 (± 12.86)	28.17 (± 20.44)	32.7 (± 13.4)	33.3 (± 10.6)

Notes:

[42] - Day 14 n = 13
Day 28 n = 10
Day 42 n = 11
Day 56 n = 10
Day 70 n = 10
Day 84 n = 10
[43] - Day 14 n = 10
Day 28 n = 8
Day 42 n = 8
Day 56 n = 7
Day 70 n = 7
Day 84 n = 6
[44] - Day 14 n = 36
Day 28 n = 33
Day 42 n = 32
Day 56 n = 31
Day 84 n = 31
[45] - Day 14 n = 4
Day 28 n = 3
Day 42 n = 4
Day 56 n = 4
Day 84 n = 4

End point values	Part B: Add-on Therapy (150 mg)	Part B: Add-on Therapy (300 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[46]	32[47]		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	38.1 (± 13.7)	38.4 (± 13.8)		
Day 14	34.1 (± 12.8)	35.2 (± 12.8)		
Day 28	33.1 (± 13.4)	36.5 (± 10.3)		
Day 42	35.5 (± 12.6)	32.7 (± 13.4)		
Day 56	30.8 (± 11.8)	32.3 (± 13.6)		
Day 70	9999 (± 9999)	9999 (± 9999)		
Day 84 (Week 12)	29.6 (± 9.2)	29.2 (± 12.4)		

Notes:

[46] - Day 14 n = 25
Day 28 n = 26
Day 42 n = 24
Day 56 n = 24
Day 84 n = 19
[47] - Day 14 n = 30
Day 28 n = 28
Day 42 n = 24
Day 56 n = 23
Day 84 n = 21

Statistical analyses

No statistical analyses for this end point

Secondary: Defeatist Performance Attitude Scale (DPAS) Scores

End point title	Defeatist Performance Attitude Scale (DPAS) Scores

End point description:

The DPAS is a 15-item, patient-rated assessment that evaluates expectations of failures or self-defeating beliefs related to prior failed experiences as well as illness on a 7-point Likert scale (total range = 15-105) ranging from totally agree (1) to totally disagree (7).

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

End point values	Part A: Monotherapy (placebo)	Part A: Monotherapy (150 mg)	Part B: Add-on Therapy (placebo)	Part B: Add-on Therapy (45 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[48]	12[49]	37[50]	5[51]
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	34.73 (± 13.92)	30.25 (± 12.43)	40.2 (± 14.6)	40.0 (± 6.4)
Day 42	40.54 (± 16.37)	27.50 (± 18.65)	37.5 (± 14.2)	39.3 (± 9.3)
Day 84 (Week 12)	38.80 (± 13.42)	16.00 (± 4.98)	36.0 (± 15.2)	54.3 (± 16.3)

Notes:

[48] - Day 42 n = 13
Day 84 n = 10
[49] - Day 42 n = 10
Day 84 n = 6
[50] - Day 42 n = 32
Day 84 n = 31
[51] - Day 42 n = 4
Day 84 n = 4

End point values	Part B: Add-on Therapy (150 mg)	Part B: Add-on Therapy (300 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[52]	32[53]		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	38.2 (± 15.9)	35.9 (± 16.2)		
Day 42	38.8 (± 16.2)	36.0 (± 16.2)		
Day 84 (Week 12)	39.0 (± 19.9)	32.2 (± 13.6)		

Notes:

[52] - Day 42 n = 24
Day 84 n = 20
[53] - Day 42 n = 26
Day 84 n = 22

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Suicidal Ideation or Behavior, and Self-injurious Behavior without Suicidal Intent on the Columbia Suicide Severity Rating Scale (C-SSRS)

End point title	Number of Participants with Suicidal Ideation or Behavior, and Self-injurious Behavior without Suicidal Intent on the Columbia Suicide Severity Rating Scale (C-SSRS)

End point description:

The C-SSRS is a suicide risk assessment tool used to help identify the risk of suicide.

End point type	Secondary

End point timeframe:

Baseline through Day 84

End point values	Part A: Monotherapy (placebo)	Part A: Monotherapy (150 mg)	Part B: Add-on Therapy (placebo)	Part B: Add-on Therapy (45 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	12	37	5
Units: Number of participants				
Suicidal ideation or behavior	0	0	1	0
Self-injurious behavior without suicidal intent	1	0	0	0

End point values	Part B: Add-on Therapy (150 mg)	Part B: Add-on Therapy (300 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	32		
Units: Number of participants				
Suicidal ideation or behavior	2	1		
Self-injurious behavior without suicidal intent	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Extrapyramidal Symptom Rating Scale, Abbreviated (ESRS-A)

End point title	Extrapyramidal Symptom Rating Scale, Abbreviated (ESRS-A)

End point description:

The ESRS-A is used to evaluate the presence and severity of extrapyramidal symptoms. Items are rated on a scale of 0 (no symptoms) to 5 (extreme symptoms).

End point type	Secondary

End point timeframe:

Baseline through Day 84

End point values	Part A: Monotherapy (placebo)	Part A: Monotherapy (150 mg)	Part B: Add-on Therapy (placebo)	Part B: Add-on Therapy (45 mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[54]	12[55]	37[56]	5[57]
Units: Units on a scale				
arithmetic mean (standard deviation)				
Akathisia Baseline	0.07 (± 0.26)	0.08 (± 0.29)	0.27 (± 0.87)	0.00 (± 0.00)
Akathisia Day 84	0.00 (± 0.00)	0.00 (± 0.00)	0.29 (± 0.94)	0.00 (± 0.00)
Dyskinesia Baseline	0.00 (± 0.00)	0.33 (± 0.89)	0.46 (± 1.95)	0.75 (± 0.96)
Dyskinesia Day 84	0.10 (± 0.32)	0.00 (± 0.00)	0.16 (± 0.90)	0.00 (± 0.00)
Dystonia Baseline	0.07 (± 0.26)	0.00 (± 0.00)	0.24 (± 0.86)	0.00 (± 0.00)
Dystonia Day 84	0.00 (± 0.00)	0.00 (± 0.00)	0.26 (± 1.03)	0.00 (± 0.00)
Parkinsonism Baseline	0.13 (± 0.52)	0.42 (± 1.00)	1.03 (± 2.36)	2.20 (± 1.92)
Parkinsonism Day 84	0.20 (± 0.63)	0.33 (± 0.82)	1.03 (± 2.87)	0.33 (± 0.58)

Notes:

[54] - Day 84 n = 10

[55] - Day 84 n = 6

[56] - Day 84 n = 31

[57] - Day 84 n = 3
Dystonia and Parkinsonism Baseline n = 5

End point values	Part B: Add-on Therapy (150 mg)	Part B: Add-on Therapy (300 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[58]	32[59]		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Akathisia Baseline	0.27 (± 0.83)	0.38 (± 0.98)		
Akathisia Day 84	0.10 (± 0.45)	0.10 (± 0.44)		
Dyskinesia Baseline	0.17 (± 0.38)	0.63 (± 1.68)		
Dyskinesia Day 84	0.15 (± 0.49)	0.29 (± 0.72)		
Dystonia Baseline	0.03 (± 0.18)	0.16 (± 0.51)		
Dystonia Day 84	0.05 (± 0.22)	0.00 (± 0.00)		
Parkinsonism Baseline	2.00 (± 3.24)	2.22 (± 4.15)		
Parkinsonism Day 84	1.15 (± 2.68)	1.00 (± 2.30)		

Notes:

[58] - Day 84 n = 20

[59] - Day 84 n = 21

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Serum Concentration (Cmax) of RO6889450

End point title	Maximum Serum Concentration (Cmax) of RO6889450[60]

End point description:

End point type	Secondary

End point timeframe:

Day 42

Notes:

[60] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was specific to study part B with the exclusion of the placebo arm as participants in that arm did not receive RO6889450.

End point values	Part B: Add-on Therapy (45 mg)	Part B: Add-on Therapy (150 mg)	Part B: Add-on Therapy (300 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	27	28	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	157 (± 58.7)	794 (± 40.3)	1550 (± 43.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve at Steady State (AUCss) of RO6889450

End point title	Area Under the Curve at Steady State (AUCss) of

End point description:

End point type	Secondary

End point timeframe:

Day 42

Notes:

[61] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was specific to study part B with the exclusion of the placebo arm as participants in that arm did not receive RO6889450.

End point values	Part B: Add-on Therapy (45 mg)	Part B: Add-on Therapy (150 mg)	Part B: Add-on Therapy (300 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	27	28	
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	2980 (± 54.8)	15100 (± 43.8)	28600 (± 48.4)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to Day 84 (Week 12)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	Part B: Add-on Therapy (placebo)
Reporting group description: Participants received placebo QD for 12 weeks in addition to their usual antipsychotic therapy.	
Reporting group title	Part B: Add-on Therapy (45 mg)
Reporting group description: Participants received 45 mg of ralmitaront QD 12 weeks in addition to their usual antipsychotic therapy (prior to protocol v5; arm was removed thereafter).	
Reporting group title	Part A: Monotherapy (150 mg)
Reporting group description: Participants received 150 mg of ralmitaront QD for 12 weeks after a 1-week washout from their usual antipsychotic therapy.	
Reporting group title	Part B: Add-on Therapy (150 mg)
Reporting group description: Participants received 150 mg of ralmitaront QD 12 weeks in addition to their usual antipsychotic therapy.	
Reporting group title	Part A: Monotherapy (placebo)
Reporting group description: Participants received placebo each day (QD) for 12 weeks after a 1-week washout from their usual antipsychotic therapy.	
Reporting group title	Part B: Add-on Therapy (300 mg)
Reporting group description: Participants received 300 mg of ralmitaront QD 12 weeks in addition to their usual antipsychotic therapy (after protocol v5).	

Serious adverse events	Part B: Add-on Therapy (placebo)	Part B: Add-on Therapy (45 mg)	Part A: Monotherapy (150 mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 37 (2.70%)	0 / 5 (0.00%)	1 / 12 (8.33%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	0 / 37 (0.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Accidental death			
subjects affected / exposed	1 / 37 (2.70%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 37 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 37 (0.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Rhinovirus infection			
subjects affected / exposed	0 / 37 (0.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part B: Add-on Therapy (150 mg)	Part A: Monotherapy (placebo)	Part B: Add-on Therapy (300 mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 30 (6.67%)	0 / 15 (0.00%)	0 / 32 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	1 / 30 (3.33%)	0 / 15 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Accidental death			

subjects affected / exposed	0 / 30 (0.00%)	0 / 15 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 30 (0.00%)	0 / 15 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 30 (3.33%)	0 / 15 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Rhinovirus infection			
subjects affected / exposed	1 / 30 (3.33%)	0 / 15 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Part B: Add-on Therapy (placebo)	Part B: Add-on Therapy (45 mg)	Part A: Monotherapy (150 mg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 37 (24.32%)	2 / 5 (40.00%)	4 / 12 (33.33%)
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 37 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Alanine aminotransferase increased			
subjects affected / exposed	0 / 37 (0.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Somnolence			
subjects affected / exposed	2 / 37 (5.41%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0

Dizziness postural			
subjects affected / exposed	0 / 37 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	1 / 37 (2.70%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	3 / 37 (8.11%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 37 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	1 / 37 (2.70%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Lip pain			
subjects affected / exposed	0 / 37 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 37 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 37 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 37 (0.00%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Rash			

subjects affected / exposed	0 / 37 (0.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Libido decreased			
subjects affected / exposed	0 / 37 (0.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	3
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 37 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 37 (5.41%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 37 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 37 (0.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 37 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Decreased appetite			
subjects affected / exposed	1 / 37 (2.70%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Part B: Add-on Therapy (150 mg)	Part A: Monotherapy (placebo)	Part B: Add-on Therapy (300 mg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 30 (26.67%)	7 / 15 (46.67%)	4 / 32 (12.50%)
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 30 (0.00%)	0 / 15 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Somnolence			
subjects affected / exposed	1 / 30 (3.33%)	0 / 15 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Dizziness postural			
subjects affected / exposed	0 / 30 (0.00%)	0 / 15 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	2 / 30 (6.67%)	0 / 15 (0.00%)	1 / 32 (3.13%)
occurrences (all)	2	0	1
Headache			
subjects affected / exposed	1 / 30 (3.33%)	0 / 15 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 30 (0.00%)	0 / 15 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	2 / 30 (6.67%)	0 / 15 (0.00%)	0 / 32 (0.00%)
occurrences (all)	2	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 15 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Lip pain			
subjects affected / exposed	0 / 30 (0.00%)	0 / 15 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 30 (0.00%)	0 / 15 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	1 / 30 (3.33%)	0 / 15 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 30 (3.33%)	0 / 15 (0.00%)	1 / 32 (3.13%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 30 (3.33%)	0 / 15 (0.00%)	2 / 32 (6.25%)
occurrences (all)	1	0	2
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Libido decreased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 30 (0.00%)	0 / 15 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 30 (10.00%)	0 / 15 (0.00%)	3 / 32 (9.38%)
occurrences (all)	3	0	3
Upper respiratory tract infection			

subjects affected / exposed	0 / 30 (0.00%)	2 / 15 (13.33%)	0 / 32 (0.00%)
occurrences (all)	0	2	0
Influenza			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 15 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 15 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			
subjects affected / exposed	1 / 30 (3.33%)	1 / 15 (6.67%)	0 / 32 (0.00%)
occurrences (all)	1	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 May 2019	Replaced IQ-PANNS with IC-PANNS. Updated eligibility criteria.
15 September 2020	Increased dose of study drug for Part B.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
18 March 2020	Recruitment was paused at all sites from 18 March 2020 to 4 November 2020 due to the COVID-19 pandemic.	04 November 2020

Notes:

Limitations and caveats

None reported