EU Clinical Trials Register

Clinical trial results:
A Phase IV, Open-label, Non-randomized, Clinical Trial to Evaluate the Safety of self-administered ADASUVE(R) (Staccato loxapine for inhalation) in Agitated Patients outside the hospital setting

Summary

EudraCT number	2015-003331-36
Trial protocol	AT NO
Global end of trial date	30 December 2019

Results information

Result version number	v1 (current)
This version publication date	11 October 2020
First version publication date	11 October 2020

Trial information

Trial identification

Sponsor protocol code	FER-Loxapine-2015-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02525991
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	FERRER INTERNACIONAL S.A.
Sponsor organisation address	Av Diagonal, 549 3rd floor, Barcelona, Spain, 08029
Public contact	Thais Baleeiro Teixeira, FERRER INTERNACIONAL S.A., 0034 935082966, tbaleeiro@ferrer.com
Scientific contact	Thais Baleeiro Teixeira, FERRER INTERNACIONAL S.A., 0034 935082966, tbaleeiro@ferrer.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	30 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 December 2019
Global end of trial reached?	Yes
Global end of trial date	30 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety profile of self-administered ADASUVE® outside the hospital setting in a population of patients that are known ADASUVE® responders and well trained on the use of the product, with a primary focus on serious adverse events (SAEs) and adverse events of special interest (AESI) related to ADASUVE®, including respiratory events.

Protection of trial subjects:

This was a prospective clinical trial study to characterize the safety profile of ADASUVE® in agitated patients when self-administered outside of a hospital setting. All patients received written and verbal information regarding the study prior to any study related procedures. The given information emphasized that participation in the study was voluntary and that the patient could withdraw from the study at any time and for any reason.
The study was conducted in compliance with the protocol, regulatory requirements, good clinical practice (GCP) and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association.

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	08 September 2016
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	Norway: 1
Country: Number of subjects enrolled	Spain: 312
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Germany: 7
Worldwide total number of subjects	322
EEA total number of subjects	322

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	317
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 323 patients were recruited, of whom one patient was not eligible, and therefore 322 were included in the study. Of these patients, 126 patients presented an agitation episode and therefore were included in the safety population. The study was conducted in 4 countries (Spain, Germany, Norway and Austria).

Pre-assignment

Screening details:

Key inclusion criteria: ≥18 years of age, diagnosis of schizophrenia or bipolar disorder, with an on-going agitation episode (mild or moderate) or with a previous one within the 6 months in the hospital setting, previously treated with ADASUVE® with a positive outcome (responders) according to CGI-I scale, and free of active respiratory disease.

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study.

Arms

Arm title	Full analysis set

Arm description:

Full analysis set (FAS) included all patients included in the study.

Arm type	Experimental
Investigational medicinal product name	Loxapine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Staccato® loxapine for Inhalation (ADASUVE®) is a single-use, hand-held, drug-device combination product that provides rapid systemic delivery by inhalation of a thermally generated aerosol of loxapine. Oral inhalation through the product initiates the controlled rapid heating of a thin film of excipient-freeloxapine to form a thermally generated, highly pure drug vapour. The vapour condenses into aerosol particles with a particle size distribution appropriate for efficient delivery to the deep lung. The rapid absorption of the drug provides peak plasma levels in the systemic circulation within minutes after administration.
ADASUVE® (loxapine) is a pre-dispensed (inhalation powder) 9.1 mg, administered using the Staccato® delivery system. Each single-dose inhaler contained 10 mg loxapine (and delivers 9.1 mg loxapine).

Number of subjects in period 1	Full analysis set
Started	322
Completed	126
Not completed	196
Patient moved to other city	1
Other reason	1

The patient did not use ADASUVE at home	1
Patient lost ADASUVE kit	2
No new episode of agitation after the 6 months	139
The patient is not eligible	6
2 agitation episodes	1
Consent withdrawn by subject	1
Suicide	1
No phone call done	1
Significantly non-compliant with the requirements	7
Patient in a long-term psychi	1
Lost to follow-up	34

Baseline characteristics

Reporting groups

Reporting group title	Overall period
Reporting group description:	
Full analysis set (FAS) included all patients included in the study.	

Reporting group values	Overall period	Total	
Number of subjects	322	322	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	317	317	
From 65-84 years	5	5	
85 years and over	0	0	
Age continuous			
Units: years			
median	40		
full range (min-max)	18 to 68	-	
Gender categorical			
Units: Subjects			
Female	126	126	
Male	195	195	
Missing	1	1	
Race			
Units: Subjects			
White/Caucasian	308	308	
American Indian/Alaskan native	2	2	
Asian/Oriental	2	2	
Black /African heritage	4	4	
Other	5	5	
Missing	1	1	
Marital status			
Units: Subjects			
Married	50	50	
Single	238	238	
Divorced	32	32	
Widow	0	0	
Missing	2	2	
Type of caregiver			
Units: Subjects			
Family caregiver	271	271	

Professional caregiver	34	34	
Neighbours or friends	14	14	
Other	2	2	
Missing	1	1	
Disease history: Diagnosis **Units: Subjects**			
Schizophrenia	171	171	
Bipolar disorder	144	144	
Other disease	6	6	
Missing	1	1	
Disease history: Number of agitation episodes within the last six months **Units: Subjects**			
0 episodes	2	2	
1 episode	72	72	
2 episodes	68	68	
3 episodes	74	74	
4 episodes	32	32	
5 episodes	20	20	
6 episodes	19	19	
7 episodes	3	3	
8 episodes	5	5	
9 episodes	1	1	
10 episodes	10	10	
12 episodes	3	3	
13 episodes	2	2	
15 episodes	1	1	
18 episodes	2	2	
20 episodes	3	3	
24 episodes	1	1	
40 episodes	1	1	
Missing	3	3	
Last agitation episode: Cause of agitation			
Cause of last agitation episode - in the last 6 months (Hospital setting)			
Units: Subjects			
Schizophrenia	168	168	
Bipolar disorder	147	147	
Other cause	4	4	
Missing	3	3	
Last agitation episode: Number of ADASUVE doses to control the episode			
Number of ADASUVE doses to control the episode - Last agitation episode in the last 6 months (Hospital setting)			
Units: Subjects			
1 dose	318	318	
Missing	4	4	
Respiratory history: Number of subjects with past or current respiratory history **Units: Subjects**			
Number of subjects with respiratory history	9	9	
Number of subjects without respiratory history	313	313	

Respiratory history: Past and current disease Units: Subjects			
Asthma	5	5	
Other: Pulmonary resection	1	1	
Other: Respiratory tract infection	1	1	
Other: Sleep apnoea syndrome	1	1	
Other: Acquired diaphragmatic eventration	1	1	
Patients without respiratory disease	313	313	

Respiratory history: Smoking habits Units: Subjects			
Non-smoker	95	95	
Ex-smoker	18	18	
Current smoker	209	209	

Medical history: Patients with any medical history condition			

In the safety population, 46 patients (36.5%) reported a total of 87 relevant medical conditions in their medical history at the baseline visit.
In the full analysis set population, 108 patients (54.0%) reported a total of 200 relevant medical conditions in their medical history at the baseline visit.

Units: Subjects			
Patients with any medical history conditions	108	108	
Patients with no medical history conditions	213	213	
Missing	1	1	

Medical history: Number of any relevant medical history conditions			

(*) Number of any MH Conditions are presented: N=87 for SAF; N=200 for FAS.

The most frequent relevant medical condition by SOC was Metabolism and nutrition disorders (2.3%) and Cardiac disorders (3.5%).

Other medical conditions by SOC included Psychiatric disorders (20% of the conditions), mainly drug abuse (6.9%) and drug dependence (4.6%); and Metabolism and nutrition disorders (11.5%) (mainly hypercholesterolemia [3.5%] and obesity [3.5%])

Units: Subjects			
Cardiac disorders	5	5	
Congenital, familial and genetic disorders	1	1	
Endocrine disorders	1	1	
Infections and infestations	4	4	
Metabolism and nutrition disorders	9	9	
Psychiatric disorders	4	4	
Renal and urinary disorders	3	3	
Respiratory, thoracic and mediastinal disorders	2	2	
Surgical and medical procedures	2	2	
Vascular disorders	4	4	
Not applicable	287	287	

Concomitant Medication: Patients with any concomitant medication			

Information only available for the safety population.

A total of 117 patients (92.9%) of the safety population received 516 concomitant medications during the study. The most used (>10%) was antipsychotic medication (48.5%), mainly olanzapine (7.0%), quetiapine (6.8%) and paliperidone (6.6%); and antiepileptics (13.2%) (clonazepam [4.3%] and valproate sodium [1.9%]) and antidepressants (10.7%). 71.5% of treatments started before baseline

visit.			
Units: Subjects			
Patients receiving concomitant medications	0	0	
Number of concomitant medications per patient: 1	0	0	
Number of concomitant medications per patient: 2	0	0	
Number of concomitant medications per patient: 3	0	0	
Number of concomitant medications per patient: 4	0	0	
Number of concomitant medications per patient: 5	0	0	
Number of concomitant medications per patient: 6	0	0	
Number of concomitant medications per patient: 7	0	0	
Number of concomitant medications per patient: 8	0	0	
Number of concomitant medications per patient: 9	0	0	
Number of concomitant medications per patient: 10	0	0	
Number of concomitant medications per patient: 12	0	0	
Not applicable	322	322	
Elegibility: Study medication at baseline			
Elegibility at baseline visit.			
Units: Subjects			
Patients receiving study medication at baseline	319	319	
Patients not receiving medication at baseline	3	3	
Elegibility: Bronchodilator at baseline			
Units: Subjects			
Patients receiving bronchodilator at baseline	321	321	
Patients not receiving bronchodilator at baseline	1	1	
Elegibility: Specific training session for the proper use of ADASUVE			
Units: Subjects			
Patients receiving training for the use of ADASUVE	321	321	
Patients not receiving training	1	1	
Elegibility: Diary card/educational material			
Units: Subjects			
Diary card/educational material delivered	320	320	
Diary card/educational material not delivered	2	2	
Elegibility: Inclusion/exclusion criteria still met at baseline			
Units: Subjects			
Inclusion/exclusion criteria still met at baseline	316	316	

Inclusion/exclusion criteria not met at baseline	6	6	

Disease history: Time from diagnosis			
Units: years			
arithmetic mean	11.17		
standard deviation	± 11.07	-	
Last agitation episode: Time from last episode			
Time from last agitation episode in the last 6 months (hospital setting)			
Units: Days			
median	14		
inter-quartile range (Q1-Q3)	6 to 39	-	
Last agitation episode: Time from last ADASUVE administration			
Time from last ADASUVE administration related to the last agitation episode - in the last 6 months (Hospital setting)			
Units: Days			
median	15		
inter-quartile range (Q1-Q3)	6 to 68	-	
Last agitation episode: Time to improvement after last ADASUVE administration			
Time to improvement after last ADASUVE administration for the last agitation episode- in the last 6 months (Hospital setting)			
Units: minute			
median	10		
inter-quartile range (Q1-Q3)	10 to 15	-	

Subject analysis sets

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety set (SAF) included all patients who received the first self-administered dose of ADASUVE® outside the hospital setting, including those who did not complete the study.

Subject analysis set title	Mild level of agitation
Subject analysis set type	Safety analysis

Subject analysis set description:

Patients with mild level of agitation based on CGI-S scale.

Subject analysis set title	Moderate level of agitation
Subject analysis set type	Safety analysis

Subject analysis set description:

Patients with moderate level of agitation based on CGI-S scale.

Subject analysis set title	Severe level of agitation
Subject analysis set type	Safety analysis

Subject analysis set description:

Patients with severe level of agitation based on CGI-S scale.

Reporting group values	Safety set	Mild level of agitation	Moderate level of agitation
Number of subjects	126	13	89

Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	123		
From 65-84 years	3		
85 years and over	0		

Age continuous Units: years			
median	38	41	38
full range (min-max)	18 to 65	25 to 65	18 to 65

Gender categorical Units: Subjects			
Female	46	4	31
Male	80	9	58
Missing	0	0	0

Race Units: Subjects			
White/Caucasian	121	12	86
American Indian/Alaskan native	0	0	0
Asian/Oriental	0	0	0
Black /African heritage	1	0	1
Other	4	1	2
Missing	0	0	0

Marital status Units: Subjects			
Married	17	3	10
Single	92	10	66
Divorced	17	0	13
Widow	0	0	0
Missing	0	0	0

Type of caregiver Units: Subjects			
Family caregiver	102	10	71
Professional caregiver	18	1	16
Neighbours or friends	4	1	2
Other	2	1	0
Missing	0		

Disease history: Diagnosis Units: Subjects			
Schizophrenia	67	6	52
Bipolar disorder	58	7	36
Other disease	1	0	1
Missing	0	0	0

Disease history: Number of agitation episodes within the last six months			

Units: Subjects			
0 episodes	0	0	0
1 episode	20	4	13
2 episodes	20	2	15
3 episodes	35	4	23
4 episodes	14	0	10
5 episodes	10	1	9
6 episodes	7	1	5
7 episodes	1	0	0
8 episodes	4	0	2
9 episodes	1	0	1
10 episodes	7	0	6
12 episodes	2	1	1
13 episodes	1	0	1
15 episodes	1	0	0
18 episodes	0	0	0
20 episodes	1	0	1
24 episodes	1	0	1
40 episodes	1	0	1
Missing	0	0	0

Last agitation episode: Cause of agitation			
Cause of last agitation episode - in the last 6 months (Hospital setting)			
Units: Subjects			
Schizophrenia	66	6	52
Bipolar disorder	57	7	35
Other cause	3	0	2
Missing	0	0	0

Last agitation episode: Number of ADASUVE doses to control the episode			
Number of ADASUVE doses to control the episode - Last agitation episode in the last 6 months (Hospital setting)			
Units: Subjects			
1 dose	126	13	89
Missing	0	0	0

Respiratory history: Number of subjects with past or current respiratory history			
Units: Subjects			
Number of subjects with respiratory history	5	0	4
Number of subjects without respiratory history	121	13	85

Respiratory history: Past and current disease			
Units: Subjects			
Asthma	2	0	2
Other: Pulmonary resection	1	0	1
Other: Respiratory tract infection	1	0	1
Other: Sleep apnoea syndrome	1	0	0
Other: Acquired diaphragmatic eventration	0	0	0
Patients without respiratory disease	121	13	85

Respiratory history: Smoking habits			
Units: Subjects			

Non-smoker	28		
Ex-smoker	9		
Current smoker	89		

Medical history: Patients with any medical history condition			

In the safety population, 46 patients (36.5%) reported a total of 87 relevant medical conditions in their medical history at the baseline visit.
In the full analysis set population, 108 patients (54.0%) reported a total of 200 relevant medical conditions in their medical history at the baseline visit.

Units: Subjects			
Patients with any medical history conditions	46		
Patients with no medical history conditions	80		
Missing	0		

Medical history: Number of any relevant medical history conditions			

(*) Number of any MH Conditions are presented: N=87 for SAF; N=200 for FAS.

The most frequent relevant medical condition by SOC was Metabolism and nutrition disorders (2.3%) and Cardiac disorders (3.5%).

Other medical conditions by SOC included Psychiatric disorders (20% of the conditions), mainly drug abuse (6.9%) and drug dependence (4.6%); and Metabolism and nutrition disorders (11.5%) (mainly hypercholesterolemia [3.5%] and obesity [3.5%])

Units: Subjects			
Cardiac disorders	3		
Congenital, familial and genetic disorders	0		
Endocrine disorders	1		
Infections and infestations	2		
Metabolism and nutrition disorders	2		
Psychiatric disorders	1		
Renal and urinary disorders	1		
Respiratory, thoracic and mediastinal disorders	1		
Surgical and medical procedures	0		
Vascular disorders	1		
Not applicable	114		

Concomitant Medication: Patients with any concomitant medication			

Information only available for the safety population.

A total of 117 patients (92.9%) of the safety population received 516 concomitant medications during the study. The most used (>10%) was antipsychotic medication (48.5%), mainly olanzapine (7.0%), quetiapine (6.8%) and paliperidone (6.6%); and antiepileptics (13.2%) (clonazepam [4.3%] and valproate sodium [1.9%]) and antidepressants (10.7%). 71.5% of treatments started before baseline visit.

Units: Subjects			
Patients receiving concomitant medications	117		
Number of concomitant medications per patient: 1	4		
Number of concomitant medications per patient: 2	12		
Number of concomitant medications per patient: 3	29		
Number of concomitant medications per patient: 4	26		

Number of concomitant medications per patient: 5	14		
Number of concomitant medications per patient: 6	17		
Number of concomitant medications per patient: 7	5		
Number of concomitant medications per patient: 8	4		
Number of concomitant medications per patient: 9	4		
Number of concomitant medications per patient: 10	1		
Number of concomitant medications per patient: 12	1		
Not applicable	0		
Elegibility: Study medication at baseline			
Elegibility at baseline visit.			
Units: Subjects			
Patients receiving study medication at baseline	125		
Patients not receiving medication at baseline	1		
Elegibility: Bronchodilator at baseline			
Units: Subjects			
Patients receiving bronchodilator at baseline	125		
Patients not receiving bronchodilator at baseline	1		
Elegibility: Specific training session for the proper use of ADASUVE			
Units: Subjects			
Patients receiving training for the use of ADASUVE	125		
Patients not receiving training	1		
Elegibility: Diary card/educational material			
Units: Subjects			
Diary card/educational material delivered	126		
Diary card/educational material not delivered	0		
Elegibility: Inclusion/exclusion criteria still met at baseline			
Units: Subjects			
Inclusion/exclusion criteria still met at baseline	126		
Inclusion/exclusion criteria not met at baseline	0		
Disease history: Time from diagnosis			
Units: years			
arithmetic mean	10.76	13.68	10.68
standard deviation	± 11.25	± 0.088	± 0.014
Last agitation episode: Time from last episode			
Time from last agitation episode in the last 6 months (hospital setting)			
Units: Days			
median	11	12	11
inter-quartile range (Q1-Q3)	4 to 31	8 to 21	4 to 37

Last agitation episode: Time from last ADASUVE administration			
Time from last ADASUVE administration related to the last agitation episode - in the last 6 months (Hospital setting)			
Units: Days			
median	14	12	14
inter-quartile range (Q1-Q3)	5 to 66	8 to 27	5 to 66
Last agitation episode: Time to improvement after last ADASUVE administration			
Time to improvement after last ADASUVE administration for the last agitation episode- in the last 6 months (Hospital setting)			
Units: minute			
median	10	10	10
inter-quartile range (Q1-Q3)	10 to 15	10 to 15	10 to 15

Reporting group values	Severe level of agitation		
Number of subjects	13		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
median	36		
full range (min-max)	18 to 65		
Gender categorical			
Units: Subjects			
Female	8		
Male	5		
Missing	0		
Race			
Units: Subjects			
White/Caucasian	12		
American Indian/Alaskan native	0		
Asian/Oriental	0		
Black /African heritage	0		
Other	1		
Missing	0		
Marital status			
Units: Subjects			
Married	3		
Single	7		
Divorced	3		

Widow	0		
Missing	0		
Type of caregiver			
Units: Subjects			
Family caregiver	11		
Professional caregiver	1		
Neighbours or friends	1		
Other	0		
Missing			
Disease history: Diagnosis			
Units: Subjects			
Schizophrenia	4		
Bipolar disorder	9		
Other disease	0		
Missing	0		
Disease history: Number of agitation episodes within the last six months			
Units: Subjects			
0 episodes	0		
1 episode	0		
2 episodes	1		
3 episodes	5		
4 episodes	2		
5 episodes	0		
6 episodes	1		
7 episodes	1		
8 episodes	2		
9 episodes	0		
10 episodes	0		
12 episodes	0		
13 episodes	0		
15 episodes	1		
18 episodes	0		
20 episodes	0		
24 episodes	0		
40 episodes	0		
Missing	0		
Last agitation episode: Cause of agitation			
Cause of last agitation episode - in the last 6 months (Hospital setting)			
Units: Subjects			
Schizophrenia	3		
Bipolar disorder	9		
Other cause	1		
Missing	0		
Last agitation episode: Number of ADASUVE doses to control the episode			
Number of ADASUVE doses to control the episode - Last agitation episode in the last 6 months (Hospital setting)			
Units: Subjects			
1 dose	13		
Missing	0		
Respiratory history: Number of subjects			

with past or current respiratory history Units: Subjects			
Number of subjects with respiratory history	0		
Number of subjects without respiratory history	13		

Respiratory history: Past and current disease Units: Subjects			
Asthma	0		
Other: Pulmonary resection	0		
Other: Respiratory tract infection	0		
Other: Sleep apnoea syndrome	0		
Other: Acquired diaphragmatic eventration	0		
Patients without respiratory disease	13		

Respiratory history: Smoking habits Units: Subjects			
Non-smoker			
Ex-smoker			
Current smoker			

Medical history: Patients with any medical history condition			

In the safety population, 46 patients (36.5%) reported a total of 87 relevant medical conditions in their medical history at the baseline visit.
In the full analysis set population, 108 patients (54.0%) reported a total of 200 relevant medical conditions in their medical history at the baseline visit.

Units: Subjects			
Patients with any medical history conditions			
Patients with no medical history conditions			
Missing			

Medical history: Number of any relevant medical history conditions			

(*) Number of any MH Conditions are presented: N=87 for SAF; N=200 for FAS.

The most frequent relevant medical condition by SOC was Metabolism and nutrition disorders (2.3%) and Cardiac disorders (3.5%).

Other medical conditions by SOC included Psychiatric disorders (20% of the conditions), mainly drug abuse (6.9%) and drug dependence (4.6%); and Metabolism and nutrition disorders (11.5%) (mainly hypercholesterolemia [3.5%] and obesity [3.5%])

Units: Subjects			
Cardiac disorders			
Congenital, familial and genetic disorders			
Endocrine disorders			
Infections and infestations			
Metabolism and nutrition disorders			
Psychiatric disorders			
Renal and urinary disorders			
Respiratory, thoracic and mediastinal disorders			
Surgical and medical procedures			
Vascular disorders			
Not applicable			

Concomitant Medication: Patients with any concomitant medication			
Information only available for the safety population. A total of 117 patients (92.9%) of the safety population received 516 concomitant medications during the study. The most used (>10%) was antipsychotic medication (48.5%), mainly olanzapine (7.0%), quetiapine (6.8%) and paliperidone (6.6%); and antiepileptics (13.2%) (clonazepam [4.3%] and valproate sodium [1.9%]) and antidepressants (10.7%). 71.5% of treatments started before baseline visit.			
Units: Subjects			
Patients receiving concomitant medications			
Number of concomitant medications per patient: 1			
Number of concomitant medications per patient: 2			
Number of concomitant medications per patient: 3			
Number of concomitant medications per patient: 4			
Number of concomitant medications per patient: 5			
Number of concomitant medications per patient: 6			
Number of concomitant medications per patient: 7			
Number of concomitant medications per patient: 8			
Number of concomitant medications per patient: 9			
Number of concomitant medications per patient: 10			
Number of concomitant medications per patient: 12			
Not applicable			
Elegibility: Study medication at baseline			
Elegibility at baseline visit.			
Units: Subjects			
Patients receiving study medication at baseline			
Patients not receiving medication at baseline			
Elegibility: Bronchodilator at baseline			
Units: Subjects			
Patients receiving bronchodilator at baseline			
Patients not receiving bronchodilator at baseline			
Elegibility: Specific training session for the proper use of ADASUVE			
Units: Subjects			
Patients receiving training for the use of ADASUVE			
Patients not receiving training			
Elegibility: Diary card/educational material			
Units: Subjects			
Diary card/educational material delivered			

Diary card/educational material not delivered			
Elegibility: Inclusion/exclusion criteria still met at baseline Units: Subjects			
Inclusion/exclusion criteria still met at baseline			
Inclusion/exclusion criteria not met at baseline			
Disease history: Time from diagnosis Units: years			
arithmetic mean	6.68		
standard deviation	± 0.011		
Last agitation episode: Time from last episode			
Time from last agitation episode in the last 6 months (hospital setting)			
Units: Days			
median	15		
inter-quartile range (Q1-Q3)	10 to 32		
Last agitation episode: Time from last ADASUVE administration			
Time from last ADASUVE administration related to the last agitation episode - in the last 6 months (Hospital setting)			
Units: Days			
median	15		
inter-quartile range (Q1-Q3)	10 to 32		
Last agitation episode: Time to improvement after last ADASUVE administration			
Time to improvement after last ADASUVE administration for the last agitation episode- in the last 6 months (Hospital setting)			
Units: minute			
median	12.5		
inter-quartile range (Q1-Q3)	10 to 22.5		

End points

End points reporting groups

Reporting group title	Full analysis set
Reporting group description:	
Full analysis set (FAS) included all patients included in the study.	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety set (SAF) included all patients who received the first self-administered dose of ADASUVE® outside the hospital setting, including those who did not complete the study.	
Subject analysis set title	Mild level of agitation
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients with mild level of agitation based on CGI-S scale.	
Subject analysis set title	Moderate level of agitation
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients with moderate level of agitation based on CGI-S scale.	
Subject analysis set title	Severe level of agitation
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients with severe level of agitation based on CGI-S scale.	

Primary: Frequency of AEs related to ADASUVE®, with focus on SAEs and AESIs (including respiratory events) following the self-administration of ADASUVE® outside of a hospital setting

End point title	Frequency of AEs related to ADASUVE®, with focus on SAEs and AESIs (including respiratory events) following the self-administration of ADASUVE® outside of a hospital setting[1]
End point description:	
The primary endpoint of the study was to assess the frequency of AEs related to ADASUVE®, with focus on SAEs and AESIs (including respiratory events) following the self-administration of ADASUVE® outside of a hospital setting.	
End point type	Primary
End point timeframe:	
All AEs related to ADASUVE after self-administration outside the hospital setting were collected.	

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: The primary safety analysis examined the frequency and percentage of patients experiencing SAEs, AESIs (e.g., respiratory AEs) and other AEs related to ADASUVE® self-administration treatment outside the hospital setting. AEs were characterized according to their severity and outcome. All AE verbatim terms were recorded and coded using Medical Dictionary for Regulatory Activities (MedDRA). AE frequency was tabulated by system organ class (SOC) and preferred term (PT) within each SOC.

End point values	Safety set			
Subject group type	Subject analysis set			
Number of subjects analysed	126			
Units: Adverse Events (AEs)				
Number of AEs	15			
Number of SAEs	1			
Number of AESIs	8			

Number of AEs related to ADASUVE	8				
Number of SAEs related to ADASUVE	0				
Number of AESIs related to ADASUVE	4				

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of other AEs-non respiratory AESIs related to ADASUVE® self-administration treatment outside the hospital setting

End point title	Incidence of other AEs-non respiratory AESIs related to ADASUVE® self-administration treatment outside the hospital setting
End point description:	

End point type	Secondary
End point timeframe:	

All AEs-non respiratory AESIs related to ADASUVE® following the self-administration outside the hospital setting were collected.

End point values	Safety set			
Subject group type	Subject analysis set			
Number of subjects analysed	126			
Units: Adverse Events (AEs)				
Number of AEs-non respiratory AESIs	2			
Number of AEs-non respiratory AESIs related to IMP	0			

Statistical analyses

No statistical analyses for this end point

Secondary: AEs, SAEs, AESIs and non-respiratory AESIs related to the second dose of ADASUVE® administered at the hospital setting

End point title	AEs, SAEs, AESIs and non-respiratory AESIs related to the second dose of ADASUVE® administered at the hospital setting
End point description:	

Incidence of AEs, SAEs, AESIs and non-respiratory AESIs related to the second dose of ADASUVE® administered at the hospital setting (only in cases with a second dose administration).

End point type	Secondary
End point timeframe:	

All AEs related to the second dose of ADASUVE administered at the hospital setting.

End point values	Safety set			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: Adverse Events (AEs)				
Number of AEs related to the second dose	0			
Number of SAEs related to the second dose	0			
Number of AESIs related to the second dose	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to improvement of the current episode of agitation: patients with controlled or uncontrolled episode

End point title	Time to improvement of the current episode of agitation: patients with controlled or uncontrolled episode
End point description:	

End point type	Secondary
End point timeframe:	

Time to onset of improvement of the current episode of agitation following the ADASUVE® self-administration outside the hospital setting

End point values	Safety set			
Subject group type	Subject analysis set			
Number of subjects analysed	126			
Units: Number of subjects				
Subjects with controlled episode	124			
Subjects with uncontrolled episode	2			
Number of ADASUVE administration at hospital	1			
Patients with any improvement	101			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to improvement of the current episode of agitation

End point title	Time to improvement of the current episode of agitation
End point description:	

End point type	Secondary

End point timeframe:

Time to onset of improvement of the current episode of agitation following the ADASUVE® self-administration outside the hospital setting

End point values	Safety set			
Subject group type	Subject analysis set			
Number of subjects analysed	126			
Units: minute				
median (inter-quartile range (Q1-Q3))				
Time to onset of improvement (minutes)	10 (10 to 20)			
Time from baseline to the episode (days)	22 (6 to 63)			

Statistical analyses

No statistical analyses for this end point

Secondary: Severity and improvement of agitation episodes

End point title	Severity and improvement of agitation episodes

End point description:

Absolute CGI-I scores up to 2 hours after drug self-administration outside of a hospital setting.
For the 20, 30 minutes and 1 and 2 hours evaluation, LOCF imputation performed.

End point type	Secondary

End point timeframe:

CGI-S was measured at follow-up visit.
CGI-I was measured at 2, 10, 20, 30 minutes and 1 and 2 hours after ADASUVE self-administration outside of a hospital setting.

End point values	Safety set			
Subject group type	Subject analysis set			
Number of subjects analysed	126			
Units: Number of subjects				
CGI-S (follow-up visit): Not assessed	8			
CGI-S (follow-up visit): Normal	0			
CGI-S (follow-up visit): Borderline mentally ill	1			
CGI-S (follow-up visit): Mildly ill	12			
CGI-S (follow-up visit): Moderately ill	52			
CGI-S (follow-up visit): Markedly ill	37			
CGI-S (follow-up visit): Severily ill	11			
CGI-S (follow-up visit): Among most extremely ill	2			
CGI-S (follow-up visit): Missing	3			
CGI-I (follow-up 2 minutes): Not assessed	17			

CGI-I (follow-up 2 minutes): Very much improved	5				
CGI-I (follow-up 2 minutes): Much improved	9				
CGI-I (follow-up 2 minutes): Minimally improved	15				
CGI-I (follow-up 2 minutes): No change	75				
CGI-I (follow-up 2 minutes): Minimally worse	1				
CGI-I (follow-up 2 minutes): Much worse	0				
CGI-I (follow-up 2 minutes): Very much worse	1				
CGI-I (follow-up 2 minutes): Missing	3				
CGI-I (follow-up 10 minutes): Not assessed	0				
CGI-I (follow-up 10 minutes): Very much improved	23				
CGI-I (follow-up 10 minutes): Much improved	43				
CGI-I (follow-up 10 minutes): Minimally improved	33				
CGI-I (follow-up 10 minutes): No change	20				
CGI-I (follow-up 10 minutes): Minimally worse	2				
CGI-I (follow-up 10 minutes): Much worse	0				
CGI-I (follow-up 10 minutes): Very much worse	0				
CGI-I (follow-up 10 minutes): Missing	5				
CGI-I (follow-up 20 minutes): Not assessed	0				
CGI-I (follow-up 20 minutes): Very much improved	40				
CGI-I (follow-up 20 minutes): Much improved	47				
CGI-I (follow-up 20 minutes): Minimally improved	27				
CGI-I (follow-up 20 minutes): No change	6				
CGI-I (follow-up 20 minutes): Minimally worse	0				
CGI-I (follow-up 20 minutes): Much worse	0				
CGI-I (follow-up 20 minutes): Very much worse	0				
CGI-I (follow-up 20 minutes): Missing	6				
CGI-I (follow-up 30 minutes): Not assessed	0				
CGI-I (follow-up 30 minutes): Very much improved	47				
CGI-I (follow-up 30 minutes): Much improved	47				
CGI-I (follow-up 30 minutes): Minimally improved	22				
CGI-I (follow-up 30 minutes): No change	3				
CGI-I (follow-up 30 minutes): Minimally worse	1				

CGI-I (follow-up 30 minutes): Much worse	0				
CGI-I (follow-up 30 minutes): Very much worse	0				
CGI-I (follow-up 30 minutes): Missing	6				
CGI-I (follow-up 1 hour): Not assessed	0				
CGI-I (follow-up 1 hour): Very much improved	54				
CGI-I (follow-up 1 hour): Much improved	42				
CGI-I (follow-up 1 hour): Minimally improved	19				
CGI-I (follow-up 1 hour): No change	5				
CGI-I (follow-up 1 hour): Minimally worse	1				
CGI-I (follow-up 1 hour): Much worse	0				
CGI-I (follow-up 1 hour): Very much worse	0				
CGI-I (follow-up 1 hour): Missing	5				
CGI-I (follow-up 2 hours): Not assessed	0				
CGI-I (follow-up 2 hours): Very much improved	61				
CGI-I (follow-up 2 hours): Much improved	35				
CGI-I (follow-up 2 hours): Minimally improved	19				
CGI-I (follow-up 2 hours): No change	5				
CGI-I (follow-up 2 hours): Minimally worse	0				
CGI-I (follow-up 2 hours): Much worse	1				
CGI-I (follow-up 2 hours): Very much worse	0				
CGI-I (follow-up 2 hours): Missing	5				

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment satisfaction and responders

End point title	Treatment satisfaction and responders

End point description:

Percentage of ADASUVE® responders, calculated as the proportion of patients who achieved a score of 1 ('very much improved') or 2 ('much improved') in CGI-Improvement scale at 2 hours after self-administration of ADASUVE®. Patients' treatment satisfaction in ADASUVE® responders measured with a 5-point Likert scale at the end of the 24-74h follow-up period.

Patients with CGI 1-2: N=96
Patients with CGI>2: N=25

End point type	Secondary

End point timeframe:

Percentage of patients with CGI-I score of 1 or 2 at 2 hours after self-administration.

End point values	Safety set			
Subject group type	Subject analysis set			
Number of subjects analysed	126			
Units: Subjects				
Patients with CGI 1-2	96			
Patients with CGI 1-2: Very dissatisfied	0			
Patients with CGI 1-2: Dissatisfied	0			
Patients with CGI 1-2: Uncertain	0			
Patients with CGI 1-2: Satisfied	58			
Patients with CGI 1-2: Very satisfied	37			
Patients with CGI 1-2: Missing	1			
Patients with CGI >2: Very dissatisfied	0			
Patients with CGI >2: Dissatisfied	1			
Patients with CGI >2: Uncertain	3			
Patients with CGI >2: Satisfied	19			
Patients with CGI >2: Very satisfied	2			
Patients with CGI >2: Missing	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-agitation medications administered at hospital setting for treating a worsening or no improvement of an agitation episode

End point title	Anti-agitation medications administered at hospital setting for treating a worsening or no improvement of an agitation episode

End point description:

Description of all anti-agitation medications administered at hospital setting (second dose of ADASUVE® or other treatments) for treating a worsening or no improvement of an agitation episode after self-administration of ADASUVE® outside the hospital setting.

End point type	Secondary

End point timeframe:

Anti-agitation medications administered at hospital setting.

End point values	Safety set			
Subject group type	Subject analysis set			
Number of subjects analysed	126			
Units: Subjects				
Patients with uncontrolled episodes	2			
Anti-agitation medication: Lorazepam 1 mg	1			
Anti-agitation medication: Asenapine Maleate 10 mg	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient-Investigator concordance

End point title	Patient-Investigator concordance

End point description:

Percentage of observed concordance and the degree of concordance between the patient/family member-caregiver and physician (clinical criteria) in identifying the severity of the agitation episode/administration of ADASUVE®.

Patient-Investigator concordance according to the Cohen's kappa coefficient was moderate (κ=0.47).

End point type	Secondary

End point timeframe:

Degree of concordance of the severity of the agitation episode between the patient/familiy member and the physician.

End point values	Safety set			
Subject group type	Subject analysis set			
Number of subjects analysed	126			
Units: Subjects				
Not assessed	1			
Mildly ill	6			
Moderately ill	32			
Borderline mentally ill	1			
Markedly ill	21			
Severy ill	7			
Among the most extremely ill	1			

Statistical analyses

No statistical analyses for this end point

Secondary: General information from patient's diary

End point title	General information from patient's diary

End point description:

Description of patients and family members/ caregivers´ demographics, and clinical characteristics of agitated patients treated with ADASUVE® outside the hospital setting.

End point type	Secondary

End point timeframe:

General information from patient's diary

End point values	Safety set			
Subject group type	Subject analysis set			
Number of subjects analysed	126			
Units: Subjects				
Person who completed the diary: Patient	72			
Person who completed the diary: Caregiver	50			
Person who completed the diary: Missing	4			
Symptoms: Worried	55			
Symptoms: Restless	82			
Symptoms: Anxious	74			
Symptoms: Grumpy	53			
Symptoms: Bad-tempered	51			
Symptoms: Tense	73			
Symptoms: Nervous	102			
Symptoms: In danger	30			
Symptoms: Frightened	36			
Symptoms: Insulting	29			
Symptoms: Other	10			
Patients with AEs 24 hours after administration	8			
Patients with medication to treat TEAEs	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Differences in patients with mild, moderate and severe levels of agitation: demographic characteristics

End point title	Differences in patients with mild, moderate and severe levels of agitation: demographic characteristics
End point description:	

End point type	Secondary
End point timeframe:	

Differences in demographics characteristics compared among mild, moderate and severe levels of agitation based on CGI-S scale.

End point values	Mild level of agitation	Moderate level of agitation	Severe level of agitation	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	89	13	
Units: Subjects				
Sex: Female	4	31	8	
Race: White/Caucasian	12	86	12	
Type of caregiver: Family caregiver	10	71	11	
Type of caregiver: Professional caregiver	1	16	1	
Type of caregiver: Neighbours or friends	1	2	1	
Type of caregiver: Other	1	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Differences in patients with mild, moderate and severe levels of agitation: age

End point title	Differences in patients with mild, moderate and severe levels of agitation: age
End point description:	

End point type	Secondary
End point timeframe:	

Differences in age compared among mild, moderate and severe levels of agitation based on CGI-S scale

End point values	Mild level of agitation	Moderate level of agitation	Severe level of agitation	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	89	13	
Units: years				
arithmetic mean (standard deviation)				
Age	44.54 (± 21.00)	38.52 (± 25.00)	36.46 (± 18.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Differences in patients with mild, moderate and severe levels of agitation: Disease history

End point title	Differences in patients with mild, moderate and severe levels of agitation: Disease history
End point description:	

End point type	Secondary

End point timeframe:

Differences in patient profile and post-treatment outcomes compared among mild, moderate and severe levels of agitation based on CGI-S scale

End point values	Mild level of agitation	Moderate level of agitation	Severe level of agitation	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	87	13	
Units: years				
arithmetic mean (standard deviation)				
Time from diagnosis (years)	13.68 (± 0.088)	10.68 (± 0.014)	6.68 (± 0.011)	

Statistical analyses

No statistical analyses for this end point

Secondary: Differences in patients with mild, moderate and severe levels of agitation: Disease history

End point title	Differences in patients with mild, moderate and severe levels of agitation: Disease history

End point description:

End point type	Secondary

End point timeframe:

Differences in disease history compared among mild, moderate and severe levels of agitation based on CGI-S scale according to patients' diary

End point values	Mild level of agitation	Moderate level of agitation	Severe level of agitation	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	89	13	
Units: Subjects				
Diagnosis: Schizophrenia	6	52	4	
Diagnosis: Bipolar disorder	7	36	9	
Diagnosis: Other disease	0	1	0	
1 agitation episode within the last 6 months	4	13	0	
2 agitation episodes within the last 6 months	2	15	1	
3 agitation episodes within the last 6 months	4	23	5	
4 agitation episodes within the last 6 months	0	10	2	
5 agitation episodes within the last 6 months	1	9	0	

6 agitation episodes within the last 6 months	1	5	1	
7 agitation episodes within the last 6 months	0	0	1	
8 agitation episodes within the last 6 months	0	2	2	
9 agitation episodes within the last 6 months	0	1	0	
10 agitation episodes within the last 6 months	0	6	0	
12 agitation episodes within the last 6 months	1	1	0	
13 agitation episodes within the last 6 months	0	1	0	
15 agitation episodes within the last 6 months	0	0	1	
20 agitation episodes within the last 6 months	0	1	0	
24 agitation episodes within the last 6 months	0	1	0	
40 agitation episodes within the last 6 months	0	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Differences in patients with mild, moderate and severe levels of agitation: last agitation episode (hospital setting)

End point title	Differences in patients with mild, moderate and severe levels of agitation: last agitation episode (hospital setting)

End point description:

End point type	Secondary

End point timeframe:

Differences in last agitation episode compared among mild, moderate and severe levels of agitation based on CGI-S scale according to patients' diary

End point values	Mild level of agitation	Moderate level of agitation	Severe level of agitation	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	89	13	
Units: Days				
median (inter-quartile range (Q1-Q3))				
Time from last episode (days)	12 (8 to 21)	11 (4 to 37)	15 (10 to 32)	
Time from last ADASUVE administration (days)	12 (8 to 27)	14 (5 to 66)	15 (10 to 32)	
Time to improvement after last administration(min)	10 (10 to 15)	10 (10 to 15)	12.5 (10 to 22.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Differences in patients with mild, moderate and severe levels of agitation: last agitation episode (hospital setting)

End point title	Differences in patients with mild, moderate and severe levels of agitation: last agitation episode (hospital setting)
End point description:	
End point type	Secondary
End point timeframe:	

Differences in last agitation episode compared among mild, moderate and severe levels of agitation based on CGI-S scale (hospital setting)

End point values	Mild level of agitation	Moderate level of agitation	Severe level of agitation	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	89	13	
Units: Subjects				
Cause of agitation: Schizophrenia	6	52	3	
Cause of agitation: Bipolar disorder	7	35	9	
Cause of agitation: Other disease	0	2	1	
1 ADASUVE dose to control the episode	13	89	13	

Statistical analyses

No statistical analyses for this end point

Secondary: Differences in patients with mild, moderate and severe levels of agitation: Disease history

End point title	Differences in patients with mild, moderate and severe levels of agitation: Disease history
End point description:	
End point type	Secondary
End point timeframe:	

Differences in past and current respiratory disease compared among mild, moderate and severe levels of agitation based on CGI-S scale according to patients' diary

End point values	Mild level of agitation	Moderate level of agitation	Severe level of agitation	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	89	13	
Units: Subjects				
Subjects with past or current respiratory disease	0	4	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Differences in patients with mild, moderate and severe levels of agitation: CGI-I evaluation

End point title	Differences in patients with mild, moderate and severe levels of agitation: CGI-I evaluation

End point description:

CGI-I was measured at 2, 10, 20, 30 minutes and 1 and 2 hours after ADASUVE self-administration outside of a hospital setting.
Absolute CGI-I scores up to 2 hours after drug self-administration outside of a hospital setting.
For the 20, 30 minutes and 1 and 2 hours evaluation, LOCF imputation performed.

End point type	Secondary

End point timeframe:

Differences in the CGI evaluation at each time-point compared among mild, moderate and severe levels of agitation based on CGI-S scale according to patients' diary

End point values	Mild level of agitation	Moderate level of agitation	Severe level of agitation	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	89	13	
Units: Subjects				
CGI-I Last agitation episode: Not assessed	2	24	1	
CGI-I Last agitation episode: Very much improved	7	21	4	
CGI-I Last agitation episode: Much improved	4	44	8	
CGI-I Last agitation episode: Minimally improved	0	0	0	
CGI-I Last agitation episode: No change	0	0	0	
CGI-I Last agitation episode: Minimally worse	0	0	0	
CGI-I Last agitation episode: Much worse	0	0	0	
CGI-I Last agitation episode: Very much worse	0	0	0	
CGI-I Last agitation episode: Missing	0	0	0	
CGI-S (follow-up): Not assessed	0	0	0	

CGI-S (follow-up): Normal	0	0	0	
CGI-S (follow-up): Borderline mentally ill	1	0	0	
CGI-S (follow-up): Mildly ill	12	0	0	
CGI-S (follow-up): Moderately ill	0	52	0	
CGI-S (follow-up): Markedly ill	0	37	0	
CGI-S (follow-up): Severity ill	0	0	11	
CGI-S (follow-up): Among the most extremely ill	0	0	2	
CGI-S (follow-up): Missing	0	0	0	
CGI-I (follow-up 2 minutes): Not assessed	0	15	0	
CGI-I (follow-up 2 minutes): Very much improved	3	1	1	
CGI-I (follow-up 2 minutes): Much improved	1	8	0	
CGI-I (follow-up 2 minutes): Minimally improved	1	12	1	
CGI-I (follow-up 2 minutes): No change	8	51	11	
CGI-I (follow-up 2 minutes): Minimally worse	0	1	0	
CGI-I (follow-up 2 minutes): Much worse	0	0	0	
CGI-I (follow-up 2 minutes): Very much worse	0	1	0	
CGI-I (follow-up 2 minutes): Missing	0	0	0	
CGI-I (follow-up 10 minutes): Not assessed	0	0	0	
CGI-I (follow-up 10 minutes): Very much improved	5	14	4	
CGI-I (follow-up 10 minutes): Much improved	1	34	5	
CGI-I (follow-up 10 minutes): Minimally improved	4	23	3	
CGI-I (follow-up 10 minutes): No change	3	15	0	
CGI-I (follow-up 10 minutes): Minimally worse	0	1	1	
CGI-I (follow-up 10 minutes): Much worse	0	0	0	
CGI-I (follow-up 10 minutes): Very much worse	0	0	0	
CGI-I (follow-up 10 minutes): Missing	0	2	0	
CGI-I (follow-up 20 minutes): Not assessed	0	0	0	
CGI-I (follow-up 20 minutes): Very much improved	4	29	5	
CGI-I (follow-up 20 minutes): Much improved	5	34	5	
CGI-I (follow-up 20 minutes): Minimally improved	3	20	3	
CGI-I (follow-up 20 minutes): No change	0	4	0	
CGI-I (follow-up 20 minutes): Minimally worse	0	0	0	
CGI-I (follow-up 20 minutes): Much worse	0	0	0	
CGI-I (follow-up 20 minutes): Very much worse	0	0	0	
CGI-I (follow-up 20 minutes): Missing	1	2	0	

CGI-I (follow-up 30 minutes): Not assessed	0	0	0	
CGI-I (follow-up 30 minutes): Very much improved	6	33	5	
CGI-I (follow-up 30 minutes): Much improved	4	35	6	
CGI-I (follow-up 30 minutes): Minimally improved	2	17	2	
CGI-I (follow-up 30 minutes): No change	0	1	0	
CGI-I (follow-up 30 minutes): Minimally worse	0	1	0	
CGI-I (follow-up 30 minutes): Much worse	0	0	0	
CGI-I (follow-up 30 minutes): Very much worse	0	0	0	
CGI-I (follow-up 30 minutes): Missing	1	2	0	
CGI-I (follow-up 1 hour): Not assessed	0	0	0	
CGI-I (follow-up 1 hour): Very much improved	7	40	5	
CGI-I (follow-up 1 hour): Much improved	2	32	5	
CGI-I (follow-up 1 hour): Minimally improved	2	14	2	
CGI-I (follow-up 1 hour): No change	1	2	0	
CGI-I (follow-up 1 hour): Minimally worse	0	0	1	
CGI-I (follow-up 1 hour): Much worse	0	0	0	
CGI-I (follow-up 1 hour): Very much worse	0	0	0	
CGI-I (follow-up 1 hour): Missing	1	1	0	
CGI-I (follow-up 2 hours): Not assessed	0	0	0	
CGI-I (follow-up 2 hours): Very much improved	7	46	6	
CGI-I (follow-up 2 hours): Much improved	2	26	4	
CGI-I (follow-up 2 hours): Minimally improved	2	14	2	
CGI-I (follow-up 2 hours): No change	1	2	0	
CGI-I (follow-up 2 hours): Minimally worse	0	0	0	
CGI-I (follow-up 2 hours): Much worse	0	0	1	
CGI-I (follow-up 2 hours): Very much worse	0	0	0	
CGI-I (follow-up 2 hours): Missing	1	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Differences in patients with mild, moderate and severe levels of agitation: Time to onset of improvement of the agitation episode after the ADASUVE® self-administration

End point title	Differences in patients with mild, moderate and severe levels of agitation: Time to onset of improvement of the agitation episode after the ADASUVE® self-administration

End point description:

End point type	Secondary

End point timeframe:

Differences in the time to onset of improvement of the current episode compared among mild, moderate and severe levels of agitation based on CGI-S scale according to patients'diary

End point values	Mild level of agitation	Moderate level of agitation	Severe level of agitation	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	89	13	
Units: Subjects				
Patients with any improvement	11	73	11	

Statistical analyses

No statistical analyses for this end point

Secondary: Differences in patients with mild, moderate and severe levels of agitation: Time to onset of improvement of the agitation episode after the ADASUVE® self-administration

End point title	Differences in patients with mild, moderate and severe levels of agitation: Time to onset of improvement of the agitation episode after the ADASUVE® self-administration

End point description:

Time to onset of improvement was calculated as the time to achieved a score 1 or 2 in the CGI scale.

End point type	Secondary

End point timeframe:

Differences in the time to onset of improvement of the current episode compared among mild, moderate and severe levels of agitation based on CGI-S scale according to patients'diary

End point values	Mild level of agitation	Moderate level of agitation	Severe level of agitation	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	89	13	
Units: Days/minutes				
median (inter-quartile range (Q1-Q3))				
Time from baseline to the episode (days)	25 (11.5 to 67)	32 (6 to 75)	14 (5 to 41)	
Time to onset of improvement (minutes)	10 (2 to 20)	10 (10 to 20)	10 (10 to 10)	

Statistical analyses

No statistical analyses for this end point

Secondary: Differences in patient profile and post-treatment outcomes compared among mild, moderate and severe levels of agitation based on CGI-S scale: Patient health status

End point title	Differences in patient profile and post-treatment outcomes compared among mild, moderate and severe levels of agitation based on CGI-S scale: Patient health status

End point description:

- General patient health status at first 3-month phone call
- General patient health status at follow-up visit with controlled episode
- General patient health status at 30-days after self-administration phone call

End point type	Secondary

End point timeframe:

Differences in the general patient status compared among mild, moderate and severe levels of agitation based on CGI-S scale according to patients' diary

End point values	Mild level of agitation	Moderate level of agitation	Severe level of agitation	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	89	13	
Units: Subjects				
First 3-month phone call: Very poor	0	0	0	
First 3-month phone call: Poor	0	2	0	
First 3-month phone call: Fair	0	2	0	
First 3-month phone call: Good	3	15	3	
First 3-month phone call: Very good	0	4	0	
First 3-month phone call: Missing	0	1	0	
Follow-up visit: Very poor	0	0	0	
Follow-up visit: Poor	0	3	3	
Follow-up visit: Fair	0	3	3	
Follow-up visit: Good	10	64	4	
Follow-up visit: Very good	3	17	3	
Follow-up visit: Missing	0	2	0	
30-days after self-administration: Very poor	0	0	0	
30-days after self-administration: Poor	1	4	0	
30-days after self-administration: Fair	0	2	1	
30-days after self-administration: Good	7	60	10	
30-days after self-administration: Very good	2	17	0	
30-days after self-administration: Missing	0	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Differences in patient profile and post-treatment outcomes compared

among mild, moderate and severe levels of agitation based on CGI-S scale: Treatment satisfaction

End point title	Differences in patient profile and post-treatment outcomes compared among mild, moderate and severe levels of agitation based on CGI-S scale: Treatment satisfaction

End point description:

End point type	Secondary

End point timeframe:

Differences in the satisfaction after self-administration of ADASUVE® outside the hospital compared among mild, moderate and severe levels of agitation based on CGI-S scale

End point values	Mild level of agitation	Moderate level of agitation	Severe level of agitation	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	89	13	
Units: Subjects				
Patients with CGI 1-2	9	72	10	
Patients with CGI 1-2: Very dissatisfied	0	0	0	
Patients with CGI 1-2: Dissatisfied	0	0	0	
Patients with CGI 1-2: Uncertain	0	0	0	
Patients with CGI 1-2: Satisfied	5	46	4	
Patients with CGI 1-2: Very satisfied	4	25	6	
Patients with CGI 1-2: Missing	0	1	0	
Patients with CGI >2: Very dissatisfied	0	0	0	
Patients with CGI >2: Dissatisfied	0	0	0	
Patients with CGI >2: Uncertain	0	1	1	
Patients with CGI >2: Satisfied	3	13	2	
Patients with CGI >2: Very satisfied	0	2	0	
Patients with CGI >2: Missing	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs that occured during the study and all SAEs that appeared after the subject had signed the informed consent form, whether or not causally related with the study drug, were recorded in detail in the subject's eCRF.

Adverse event reporting additional description:

AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) system and tabulated by SOC and by Preferred Term (PT).
The adverse events analysis examined data collected during the study period immediately following ADASUVE® self-administration outside of a hospital setting for all enrolled patients.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Safety set

Reporting group description:

Safety set (SAF) included all patients who received the first self-administered dose of ADASUVE® outside the hospital setting, including those who did not complete the study.

Reporting group title	Full analysis set

Reporting group description:

Full analysis set (FAS) included all patients included in the study.

Serious adverse events	Safety set	Full analysis set	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 126 (0.79%)	4 / 322 (1.24%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Phlebitis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Stroke			
subjects affected / exposed	0 / 126 (0.00%)	1 / 322 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			

	subjects affected / exposed	1 / 126 (0.79%)	1 / 322 (0.31%)	
	occurrences causally related to treatment / all	0 / 1	0 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Asthmatic attack				
	subjects affected / exposed	0 / 126 (0.00%)	1 / 322 (0.31%)	
	occurrences causally related to treatment / all	0 / 0	0 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders				
Suicide				
	subjects affected / exposed	0 / 126 (0.00%)	1 / 322 (0.31%)	
	occurrences causally related to treatment / all	0 / 0	0 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations				
Pneumonia				
	subjects affected / exposed	0 / 126 (0.00%)	1 / 322 (0.31%)	
	occurrences causally related to treatment / all	0 / 0	0 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Safety set	Full analysis set	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 126 (9.52%)	12 / 322 (3.73%)	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	3 / 126 (2.38%)	3 / 322 (0.93%)	
occurrences (all)	3	3	
Dizziness			
subjects affected / exposed	1 / 126 (0.79%)	1 / 322 (0.31%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Feeling cold			
subjects affected / exposed	1 / 126 (0.79%)	1 / 322 (0.31%)	
occurrences (all)	1	1	
Drug ineffective			

subjects affected / exposed	1 / 126 (0.79%)	1 / 322 (0.31%)	
occurrences (all)	1	1	

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 126 (3.17%)	4 / 322 (1.24%)	
occurrences (all)	4	4	
Respiratory failure			
subjects affected / exposed	1 / 126 (0.79%)	1 / 322 (0.31%)	
occurrences (all)	1	1	
Wheezing			
subjects affected / exposed	1 / 126 (0.79%)	1 / 322 (0.31%)	
occurrences (all)	1	1	

Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 126 (0.79%)	1 / 322 (0.31%)	
occurrences (all)	1	1	

Psychiatric disorders			
Intentional self-injury			
subjects affected / exposed	1 / 126 (0.79%)	1 / 322 (0.31%)	
occurrences (all)	1	1	

Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	1 / 126 (0.79%)	1 / 322 (0.31%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 October 2015	In this amendment (19 October 2015), the beta-agonist bronchodilator used in the study was precisely named in the protocol (salbutamol), as a request of the German Ethics Committee.
18 December 2015	After reviewing the clarifications received by the Clinical Research Ethics Committees from Spain, in this amendment (18 December 2015) it was decided to amend certain sections of the protocol to clarify some important aspects of the inclusion criteria and the conduct of the Amendment number 3 to the protocol.
17 May 2016	In this amendment (17 May 2016) the sponsor decided to amend certain sections of the protocol to confirm the agitation episode would be reliable recognized and managed correctly by the patient/caregiver; better understanding of the target population for the use of ADASUVE® in an outside hospital setting.
01 March 2017	In this amendment (1 March 2017) the sponsor decided to amend certain sections of the protocol to notify the extension of the patient inclusion period as well rectify some protocol sections to be congruent with inclusion/ exclusion criteria, which were already approved in the previous protocol version.
11 October 2017	The main reason for this amendment (11 October 2017) was the change of the coordinating investigator. The former coordinating investigator Dr. Andrés Fontalba left the hospital where the study was approved due to personal reasons. Additionally, and for safety purposes, an interim analysis was planned when data for approximately 50 patients who completed the study were available. Also, the number of centres and participating countries and anticipated study period was updated according to feasibility and study recruitment status.
02 July 2018	The main reason for this amendment (2 July 2018) was the discontinuation of the Norway centre participation. In a subsequent modification of the amendment (30 July 2018), Norway was again listed among the participant countries. Additionally, the anticipated study period was updated according to feasibility and study recruitment status. Also, the marketing authorization holder details were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Although the expected sample size was of 500 patients, with the 323 patients included in the study the upper limit of the 95% CI is between 0,010 and 0,012. Thus, with this number of patients we can discard the prevalence of bronchospasm of 1.0−1.2%.

Notes: