Clinical trial results:
Efficacy and safety of inhaled loxapine compared with IM antipsychotic in acutely agitated patients with schizophrenia or bipolar disorder

Summary

EudraCT number	2014-000456-29
Trial protocol	CZ ES DE
Global end of trial date	31 October 2016

Results information

Result version number	v1 (current)
This version publication date	15 November 2017
First version publication date	15 November 2017

Trial information

Trial identification

Sponsor protocol code	FCD-ADA-1401

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1201-3658

Notes:

Sponsors

Sponsor organisation name	Ferrer Internacional, S.A.
Sponsor organisation address	Avenida Diagonal 549, Barcelona, Spain, 08029
Public contact	Clinical Development, Ferrer Internacional, S.A., +34 93 600 37 00, desarrollo.clinico@ferrer.com
Scientific contact	Clinical Development, Ferrer Internacional, S.A., +34 93 600 37 00, desarrollo.clinico@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	31 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 October 2016
Global end of trial reached?	Yes
Global end of trial date	31 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy, defined as time to response (where response is defined as a Clinical Global Impression of Improvement [CGI I] score of 1 ["Very much improved"] or 2 ["Much improved"]), of inhaled loxapine 9.1 mg as compared with aripiprazole 9.75 mg administered as an intramuscular (IM) injection in acutely agitated patients with schizophrenia or bipolar disorder.

Protection of trial subjects:

This study was conducted in compliance with Independent Ethics Committee and International Council of Harmonisation Good Clinical Practice Guidelines, in accordance with applicable regulations regarding clinical safety data management (E2A, E2B(R3)), European Community directives 2001/20, 2001/83, 2003/94, and 2005/28 as enacted into local law, and with ICH guidelines regarding scientific integrity (E4, E8, E9, and E10). In addition, this study adhered to all local regulatory requirements, and requirements for data protection.

Background therapy:

No background therapies were to be used by patients in both treatment groups.

The use of benzodiazepines or other hypnotics or oral or short-acting IM antipsychotics was not permitted within 4 hours (Protocol Versions 1.0, 2.0, and 3.0) or 1 hour (Protocol Versions 4.0 and 5.0) prior to study drug administration or during the study. The only exception was benzodiazepines when used as rescue medication, as described below.

If required, rescue medication could be used as per physician judgement and usual clinical practice and when dosed as clinically indicated. Rescue medication constituted 2 mg of IM or oral lorazepam (or an equivalent dose of other benzodiazepine). Unless medically required, rescue medication was not used until after:

- At least 2 hours post Dose 1
- 2-hour efficacy assessments had been completed
- Dose 2 of the study medication had been given
- At least 20 minutes had elapsed after the administration of study medication
- The corresponding evaluation had been performed.

Evidence for comparator:

Aripiprazole for IM injection was selected as the active comparator for use in this study. It is a recognised standard of care for the rapid control of agitation and disturbed behaviours in patients with schizophrenia or in patients with bipolar I disorder, when oral therapy is not available.

Actual start date of recruitment	02 December 2014
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	Spain: 110
Country: Number of subjects enrolled	Czech Republic: 18

Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Russian Federation: 230
Worldwide total number of subjects	359
EEA total number of subjects	129

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)	357
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled into the study from 02 December 2014 to 30 September 2016. A total of 23 centres in four countries enrolled a total of 359 patients: 18 patients at 4 centres in the Czech Republic; 1 patient at 1 centre in Germany; 230 patients at 9 centres in Russia; and 110 patients at 9 centres in Spain.

Pre-assignment

Screening details:

The Pre-treatment Period (included screening of up to 4 hours and baseline up to 30 minutes prior to the administration of initial study medication). A total of 372 patients were screened.

Pre-assignment period milestones

Number of subjects started	372[1]
Number of subjects completed	359

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did not fulfill inclusion criterion 4: 1
Reason: Number of subjects	Did not fulfill inclusion criterion 3: 2
Reason: Number of subjects	Absence of study medication: 1
Reason: Number of subjects	Insufficient medication (aripiprazole): 1
Reason: Number of subjects	Lack of study medication: 1
Reason: Number of subjects	Lack of suitable medication: 1
Reason: Number of subjects	Patient withdrew consent prior to randomisation: 1
Reason: Number of subjects	Randomisation stopped by Sponsor: 1
Reason: Number of subjects	The system did not provide medication kits: 1
Reason: Number of subjects	Insufficient medication at centre to randomise: 2
Reason: Number of subjects	Fulfilled exclusion criterion 4: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The pre-assignment period included all screened patients; 359 patients were randomized (period 1: Randomisation); 357 patients were randomized with informed consent (period 2: Baseline [FAS]).

Period 1

Period 1 title	Randomisation
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[2]

Blinding implementation details:

Inhaled loxapine and aripiprazole were administered open-label. Efficacy assessments (CGI-I and CGI of severity [CGI-S]) for the primary end point and Treatment Satisfaction for Medication Questionnaire (TSQM; Item 14) were performed by a trained blinded assessor. To maintain assessor blinding, a different staff member administered the study treatment. The assessor role was restricted to efficacy assessments. Patients were told not to tell the blinded assessor which treatment they received.

Arms

Are arms mutually exclusive?	Yes

Arm title	Inhaled loxapine (Randomisation)

Arm description:

This arm comprised patients randomised to receive inhaled loxapine 9.1 mg.

Arm type	Experimental
Investigational medicinal product name	Inhaled loxapine
Investigational medicinal product code	ATC: N05AH01
Other name	Adasuve®
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

The dose of inhaled loxapine was 9.1 mg. Patients randomised to inhaled loxapine received one or two doses of inhaled loxapine during the study; all patients randomised to inhaled loxapine were to receive Dose 1, and Dose 2, a pro re nata (PRN) dose, could be administered ≥ 2 hours after Dose 1 if agitation did not subside sufficiently after the first dose of study medication or in case of agitation recurrence.

Loxapine was administered by inhalation using a thermally-generated aerosol (Staccato delivery system). Loxapine was provided in a single-dose inhaler, packaged in a sealed pouch within a carton and had to remain in the original pouch until ready for use in order to protect from light and moisture.

Arm title	Aripiprazole (Randomisation)

Arm description:

This arm comprised patients randomised to receive aripiprazole 9.75 mg.

Arm type	Active comparator
Investigational medicinal product name	Aripiprazole
Investigational medicinal product code	ATC: N05AX12
Other name	Abilify®
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The dose of aripiprazole was 9.75 mg. Patients randomised to aripiprazole received one or two doses of IM aripiprazole during the study; all patients randomised to aripiprazole were to receive Dose 1, and Dose 2, a PRN dose, could be administered ≥ 2 hours after Dose 1 if agitation did not subside sufficiently after the first dose of study medication or in case of agitation recurrence.

Aripiprazole (Abilify®) was commercially available and was purchased directly from the supplier and supplied to sites by Almac. Aripiprazole solution for IM injection was provided in a vial and packaged within a carton. The vial containing aripiprazole had to be kept in the outer carton in order to protect it from light.

Notes:

[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This was an open-label assessor-blind, randomised, active control trial.

Number of subjects in period 1	Inhaled loxapine (Randomisation)	Aripiprazole (Randomisation)
Started	179	180
Completed	179	178
Not completed	0	2
Did not give informed consent	-	2

Period 2

Period 2 title	Baseline (FAS)
Is this the baseline period?	Yes[3]
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[4]

Blinding implementation details:

Inhaled loxapine and aripiprazole were supplied as open-label medication. The efficacy assessments (CGI-I and CGI-S) for the primary end point and Item 14 of the TSQM were performed by a blinded assessor trained on the protocol. In order to maintain assessor blinding, a different staff member administered the study treatment. The role of the assessor was restricted to the efficacy assessments. Patients were instructed not to tell the blinded assessor which treatment they received.

Arms

Are arms mutually exclusive?	Yes
Arm title	Inhaled loxapine (Baseline)

Arm description:

The inhaled loxapine Full Analysis Set (FAS) included all patients randomised to inhaled loxapine with informed consent, regardless of whether or not the patients went on to receive Dose 1. All efficacy analyses and all efficacy and baseline summaries were performed on the FAS. Patients in the FAS were categorised based on the treatment to which they were randomised, irrespective of the actual treatment received.

Arm type	Experimental
Investigational medicinal product name	Inhaled loxapine
Investigational medicinal product code	ATC: N05AH01
Other name	Adasuve®
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

The dose of inhaled loxapine was 9.1 mg. Patients randomised to inhaled loxapine received one or two doses of inhaled loxapine during the study; all patients randomised to inhaled loxapine were to receive Dose 1, and Dose 2, a PRN dose, could be administered ≥ 2 hours after Dose 1 if agitation did not subside sufficiently after the first dose of study medication or in case of agitation recurrence.

Loxapine was administered by inhalation using a thermally-generated aerosol (Staccato delivery system). Loxapine was provided in a single-dose inhaler, packaged in a sealed pouch within a carton and had to remain in the original pouch until ready for use in order to protect from light and moisture.

Arm title	Aripiprazole (Baseline)

Arm description:

The aripiprazole FAS included all patients randomised to aripiprazole with informed consent, regardless of whether or not the patients went on to receive Dose 1. All efficacy analyses and all efficacy and baseline summaries were performed on the FAS. Patients in the FAS were categorised based on the treatment to which they were randomised, irrespective of the actual treatment received.

Arm type	Active comparator
Investigational medicinal product name	Aripiprazole
Investigational medicinal product code	ATC: N05AX12
Other name	Abilify®
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The dose of aripiprazole was 9.75 mg. Patients randomised to aripiprazole received one or two doses of IM aripiprazole during the study; all patients randomised to aripiprazole were to receive Dose 1, and Dose 2, a PRN dose, could be administered ≥ 2 hours after Dose 1 if agitation did not subside sufficiently after the first dose of study medication or in case of agitation recurrence.

Aripiprazole (Abilify®) was commercially available and was purchased directly from the supplier and supplied to sites by Almac. Aripiprazole solution for IM injection was provided in a vial and packaged within a carton. The vial containing aripiprazole had to be kept in the outer carton in order to protect it from light.

Notes:

[3] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 (randomisation) included 2 patients randomised in the aripiprazole group who did not provide informed consent. The 2 patients did not receive treatment and they were not included in the analyses. Therefore, Period 1 was not considered the baseline period in this study.

[4] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This was an open-label assessor-blind, randomised, active control trial.

Number of subjects in period 2[5]	Inhaled loxapine (Baseline)	Aripiprazole (Baseline)
Started	179	178
Completed	179	178

Notes:

[5] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline (FAS) includes all randomised patients who provided informed consent. There were 2 patients randomised in the aripiprazole group (and hence included in Period 1 [randomization]) who did not provide informed consent. The 2 patients are not included in the Baseline (FAS) period (Period 2).

Period 3

Period 3 title	Post-treatment Evaluation Period (FAS)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[6]

Blinding implementation details:

Inhaled loxapine and aripiprazole were supplied as open-label medication. The efficacy assessment (CGI-I) for the primary end point and Item 14 of the TSQM were performed by a blinded assessor trained on the protocol. In order to maintain assessor blinding, a different staff member administered the study treatment. The role of the assessor was restricted to the efficacy assessments. Patients were instructed not to tell the blinded assessor which treatment they received.

Arms

Are arms mutually exclusive?	Yes
Arm title	Inhaled loxapine (FAS)

Arm description:

The inhaled loxapine FAS included all patients randomised to inhaled loxapine with informed consent, regardless of whether or not the patients went on to receive Dose 1. All efficacy analyses and all efficacy and baseline summaries were performed on the FAS. Patients in the FAS were categorised based on the treatment to which they were randomised, irrespective of the actual treatment received.

Arm type	Experimental
Investigational medicinal product name	Inhaled loxapine
Investigational medicinal product code	ATC: N05AH01
Other name	Adasuve®
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

The dose of inhaled loxapine was 9.1 mg. Patients randomised to inhaled loxapine received one or two doses of inhaled loxapine during the study; all patients randomised to inhaled loxapine were to receive Dose 1, and Dose 2, a PRN dose, could be administered ≥ 2 hours after Dose 1 if agitation did not subside sufficiently after the first dose of study medication or in case of agitation recurrence.

Loxapine was administered by inhalation using a thermally-generated aerosol (Staccato delivery system). Loxapine was provided in a single-dose inhaler, packaged in a sealed pouch within a carton and had to remain in the original pouch until ready for use in order to protect from light and moisture.

Arm title	Aripiprazole (FAS)

Arm description:

The aripiprazole FAS included all patients randomised to aripiprazole with informed consent, regardless of whether or not the patients went on to receive Dose 1. All efficacy analyses and all efficacy and baseline summaries were performed on the FAS. Patients in the FAS were categorised based on the treatment to which they were randomised, irrespective of the actual treatment received.

Arm type	Active comparator
Investigational medicinal product name	Aripiprazole
Investigational medicinal product code	ATC: N05AX12
Other name	Abilify®
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The dose of aripiprazole was 9.75 mg. Patients randomised to aripiprazole received one or two doses of IM aripiprazole during the study; all patients randomised to aripiprazole were to receive Dose 1, and Dose 2, a PRN dose, could be administered ≥ 2 hours after Dose 1 if agitation did not subside sufficiently after the first dose of study medication or in case of agitation recurrence.

Aripiprazole (Abilify®) was commercially available and was purchased directly from the supplier and supplied to sites by Almac. Aripiprazole solution for IM injection was provided in a vial and packaged within a carton. The vial containing aripiprazole had to be kept in the outer carton in order to protect it from light.

Notes:

[6] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This was an open-label assessor-blind, randomised, active control trial.

Number of subjects in period 3	Inhaled loxapine (FAS)	Aripiprazole (FAS)
Started	179	178
Completed	173	171
Not completed	6	7
Consent withdrawn by subject	2	1
Physician decision	2	-
Adverse event, non-fatal	2	6

Baseline characteristics

Reporting groups	
Reporting group title	Inhaled loxapine (Baseline)

Reporting group description:

The inhaled loxapine Full Analysis Set (FAS) included all patients randomised to inhaled loxapine with informed consent, regardless of whether or not the patients went on to receive Dose 1. All efficacy analyses and all efficacy and baseline summaries were performed on the FAS. Patients in the FAS were categorised based on the treatment to which they were randomised, irrespective of the actual treatment received.

Reporting group title	Aripiprazole (Baseline)

Reporting group description:

The aripiprazole FAS included all patients randomised to aripiprazole with informed consent, regardless of whether or not the patients went on to receive Dose 1. All efficacy analyses and all efficacy and baseline summaries were performed on the FAS. Patients in the FAS were categorised based on the treatment to which they were randomised, irrespective of the actual treatment received.

Reporting group values	Inhaled loxapine (Baseline)	Aripiprazole (Baseline)	Total
Number of subjects	179	178	357
Age categorical			
Patients eligible for inclusion in the study were to be between the ages of 18 to 65 years, inclusive.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	178	177	355
From 65-84 years	1	1	2
85 years and over	0	0	0
Age continuous			
Patients eligible for inclusion in the study were to be between the ages of 18 to 65 years, inclusive.			
Units: years			
arithmetic mean	40.44	40.26	
standard deviation	± 11.71	± 11.66	-
Gender categorical			
Units: Subjects			
Female	82	94	176
Male	97	84	181
Race			
Units: Subjects			
Asian	1	1	2
Multiple	0	1	1
Native Hawaiian or Other Pacific Islands	0	1	1
Other	1	0	1
White	177	175	352
Disease Type			

Units: Subjects			
Bipolar I Disorder	30	30	60
Schizophrenia	149	148	297

Subject analysis sets

Subject analysis set title	Inhaled Loxapine (Safety Set)
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Set included all enrolled patients who had taken Dose 1. All safety analyses were performed on the Safety Set. Patients in the Safety Set were categorised based on the actual treatment the patients received, irrespective of the treatment to which they were randomised.

Subject analysis set title	Aripiprazole (Safety Set)
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Set included all enrolled patients who had taken Dose 1. All safety analyses were performed on the Safety Set. Patients in the Safety Set were categorised based on the actual treatment the patients received, irrespective of the treatment to which they were randomised.

Subject analysis set title	Total (Safety Set)
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Set included all enrolled patients who had taken Dose 1. All safety analyses were performed on the Safety Set. Patients in the Safety Set were categorised based on the actual treatment the patients received, irrespective of the treatment to which they were randomised.

Subject analysis set title	Total (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS included all patients randomised to inhaled loxapine with informed consent, regardless of whether or not the patients went on to receive Dose 1. All efficacy analyses and all efficacy and baseline summaries were performed on the FAS. Patients in the FAS were categorised based on the treatment to which they were randomised, irrespective of the actual treatment received.

Reporting group values	Inhaled Loxapine (Safety Set)	Aripiprazole (Safety Set)	Total (Safety Set)
Number of subjects	179	177	356
Age categorical			
Patients eligible for inclusion in the study were to be between the ages of 18 to 65 years, inclusive.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	178	176	354
From 65-84 years	1	1	2
85 years and over	0	0	0
Age continuous			
Patients eligible for inclusion in the study were to be between the ages of 18 to 65 years, inclusive.			
Units: years			
arithmetic mean	40.44	40.28	40.36
standard deviation	± 11.71	± 11.69	± 11.68

Gender categorical Units: Subjects			
Female	82	94	176
Male	97	83	180
Race Units: Subjects			
Asian	1	1	2
Multiple	0	1	1
Native Hawaiian or Other Pacific Islands	0	1	1
Other	1	0	1
White	177	174	351
Disease Type Units: Subjects			
Bipolar I Disorder	30	30	60
Schizophrenia	149	147	296

Reporting group values	Total (FAS)		
Number of subjects	357		
Age categorical			
Patients eligible for inclusion in the study were to be between the ages of 18 to 65 years, inclusive.			
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)	355		
From 65-84 years	2		
85 years and over	0		
Age continuous			
Patients eligible for inclusion in the study were to be between the ages of 18 to 65 years, inclusive.			
Units: years			
arithmetic mean	40.35		
standard deviation	± 11.67		
Gender categorical Units: Subjects			
Female	176		
Male	181		
Race Units: Subjects			
Asian	2		
Multiple	1		
Native Hawaiian or Other Pacific Islands	1		
Other	1		
White	352		
Disease Type Units: Subjects			

Bipolar I Disorder Schizophrenia	60 297		

End points

End points reporting groups

Reporting group title	Inhaled loxapine (Randomisation)
Reporting group description:	
This arm comprised patients randomised to receive inhaled loxapine 9.1 mg.	
Reporting group title	Aripiprazole (Randomisation)
Reporting group description:	
This arm comprised patients randomised to receive aripiprazole 9.75 mg.	
Reporting group title	Inhaled loxapine (Baseline)
Reporting group description:	
The inhaled loxapine Full Analysis Set (FAS) included all patients randomised to inhaled loxapine with informed consent, regardless of whether or not the patients went on to receive Dose 1. All efficacy analyses and all efficacy and baseline summaries were performed on the FAS. Patients in the FAS were categorised based on the treatment to which they were randomised, irrespective of the actual treatment received.	
Reporting group title	Aripiprazole (Baseline)
Reporting group description:	
The aripiprazole FAS included all patients randomised to aripiprazole with informed consent, regardless of whether or not the patients went on to receive Dose 1. All efficacy analyses and all efficacy and baseline summaries were performed on the FAS. Patients in the FAS were categorised based on the treatment to which they were randomised, irrespective of the actual treatment received.	
Reporting group title	Inhaled loxapine (FAS)
Reporting group description:	
The inhaled loxapine FAS included all patients randomised to inhaled loxapine with informed consent, regardless of whether or not the patients went on to receive Dose 1. All efficacy analyses and all efficacy and baseline summaries were performed on the FAS. Patients in the FAS were categorised based on the treatment to which they were randomised, irrespective of the actual treatment received.	
Reporting group title	Aripiprazole (FAS)
Reporting group description:	
The aripiprazole FAS included all patients randomised to aripiprazole with informed consent, regardless of whether or not the patients went on to receive Dose 1. All efficacy analyses and all efficacy and baseline summaries were performed on the FAS. Patients in the FAS were categorised based on the treatment to which they were randomised, irrespective of the actual treatment received.	
Subject analysis set title	Inhaled Loxapine (Safety Set)
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Set included all enrolled patients who had taken Dose 1. All safety analyses were performed on the Safety Set. Patients in the Safety Set were categorised based on the actual treatment the patients received, irrespective of the treatment to which they were randomised.	
Subject analysis set title	Aripiprazole (Safety Set)
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Set included all enrolled patients who had taken Dose 1. All safety analyses were performed on the Safety Set. Patients in the Safety Set were categorised based on the actual treatment the patients received, irrespective of the treatment to which they were randomised.	
Subject analysis set title	Total (Safety Set)
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Set included all enrolled patients who had taken Dose 1. All safety analyses were performed on the Safety Set. Patients in the Safety Set were categorised based on the actual treatment the patients received, irrespective of the treatment to which they were randomised.	
Subject analysis set title	Total (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS included all patients randomised to inhaled loxapine with informed consent, regardless of	

whether or not the patients went on to receive Dose 1. All efficacy analyses and all efficacy and baseline summaries were performed on the FAS. Patients in the FAS were categorised based on the treatment to which they were randomised, irrespective of the actual treatment received.

Primary: Time to response, where response was defined as a CGI-I score of 1 ("Very much improved") or 2 ("Much improved")

End point title	Time to response, where response was defined as a CGI-I score of 1 ("Very much improved") or 2 ("Much improved")

End point description:

The primary efficacy end point was the time from Dose 1 to response in minutes, where response was defined as a CGI I score of 1 (“Very much improved”) or 2 (“Much improved”). CGI-I score was assessed at 10, 20, 30, 50, 60, 90 and 120 minutes post Dose 1. Patients without response within 2 hours were considered as non-responders and the “time to response” as 4 hours (2 more than the maximum follow up for this variable). The analysis of primary efficacy variables was performed by means of suitable descriptive analysis and the inferential analysis was performed by the Hodges-Lehmann approach based on the Wilcoxon log-rank (a.k.a Mann-Whitney).

End point type	Primary

End point timeframe:

The primary end point was assessed at 10, 20, 30, 50, 60, 90 and 120 minutes post Dose 1 during the Post-treatment Evaluation Period.

End point values	Inhaled loxapine (FAS)	Aripiprazole (FAS)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	178		
Units: Minutes				
median (confidence interval 95%)	50 (30 to 50)	60 (50 to 90)		

Attachments (see zip file)	Kaplan-Meier Plot of Time to CGI-I Response (FAS)

Statistical analyses

Statistical analysis title	Wilcoxon Log-Rank test

Statistical analysis description:

The primary efficacy analysis was performed on the time to response for all patients in the FAS using a Wilcoxon rank-sum test. Patients who withdrew early from the study, or patients who completed the study through to 24 hours without meeting the response criteria, were censored at their last CGI I assessment time and classed as non-responders in the primary efficacy analysis.

Comparison groups	Inhaled loxapine (FAS) v Aripiprazole (FAS)
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0005
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	10

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	30

Notes:

[1] - The null hypothesis stated that there was no difference in time to response between inhaled loxapine and aripiprazole, with the alternative of a non-zero difference between groups. The primary treatment comparison was evaluated using a two-sided significance level of 0.05. The primary objective was met if the results of this analysis showed significant superiority, from a Wilcoxon rank-sum test, in the time to response of the inhaled loxapine versus aripiprazole groups over 2 hours.

Secondary: The proportion of responders, as defined by a CGI I score of 1 or 2 at 10, 20, 30, 50, 60, 90 and 120 minutes after the first dose of study drug administration

End point title	The proportion of responders, as defined by a CGI I score of 1 or 2 at 10, 20, 30, 50, 60, 90 and 120 minutes after the first dose of study drug administration

End point description:

This end point comprised the:

- Percentage of responders by assessment timepoint: Percentage of responders out of all patients in the Full Analysis Set (FAS) at 10, 20, 30, 50, 60, 90 and 120 minutes post Dose 1, where response was defined as a CGI-I score of 1 (“Very much improved”) or 2 (“Much improved”).
- Percentage of cumulative responders by assessment timepoint: Percentage of cumulative responders out of all patients in the FAS at 10, 20, 30, 50, 60, 90 and 120 minutes post Dose 1, where response was defined as a CGI-I score of 1 (“Very much improved”) or 2 (“Much improved”).

Patients who did not record CGI-I information at any time point, or who did not meet the response criteria at any of the assessments, were classed as non-responders.

The numerators for the percentages are presented in the end point below.

End point type	Secondary

End point timeframe:

This secondary exploratory end point was assessed at 10, 20, 30, 50, 60, 90 and 120 minutes post-Dose 1.

End point values	Inhaled loxapine (FAS)	Aripiprazole (FAS)	Total (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	179	178	357	
Units: % patients				
Percent responders (10 min)	14	4	9	
Percent responders (20 min)	30	9	19	
Percent responders (30 min)	43	24	33	
Percent responders (50 min)	57	44	50	
Percent responders (60 min)	69	54	62	
Percent responders (90 min)	76	71	74	
Percent responders (120 min)	79	78	78	
Cumulative percent responders (10 min)	14	4	9	
Cumulative percent responders (20 min)	30	10	20	
Cumulative percent responders (30 min)	43	25	34	
Cumulative percent responders (50 min)	58	46	52	
Cumulative percent responders (60 min)	70	56	63	
Cumulative percent responders (90 min)	80	74	77	
Cumulative percent responders (120 min)	84	83	84	

Statistical analyses

Statistical analysis title	Chi-Squared Test

Statistical analysis description:

Secondary inferential analyses were performed using two group Chi-squared tests and were exploratory in nature. All statistical tests were applied with a 0.05 two-sided significance level.

Comparison groups	Inhaled loxapine (FAS) v Aripiprazole (FAS)
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7763 [2]
Method	Chi-squared

Notes:

[2] - The proportion/cumulative proportion of CGI-I responders were significantly greater in the inhaled loxapine vs aripiprazole group at 10, 20, 30, 50, and 60 min post treatment ($p<0.05$); at 90 min: p=0. 3207/p=0.1560; and at 120 min: p=0.7763/p=0.6520.

Secondary: The number of responders, as defined by a CGI I score of 1 or 2 at 10, 20, 30, 50, 60, 90 and 120 minutes after the first dose of study drug administration

End point title	The number of responders, as defined by a CGI I score of 1 or 2 at 10, 20, 30, 50, 60, 90 and 120 minutes after the first dose of study drug administration

End point description:

This end point comprised the:

- Percentage of responders by assessment timepoint: Percentage of responders out of all patients in the Full Analysis Set (FAS) at 10, 20, 30, 50, 60, 90 and 120 minutes post Dose 1, where response was defined as a CGI-I score of 1 (“Very much improved”) or 2 (“Much improved”).
- Percentage of cumulative responders by assessment timepoint: Percentage of cumulative responders out of all patients in the FAS at 10, 20, 30, 50, 60, 90 and 120 minutes post Dose 1, where response was defined as a CGI-I score of 1 (“Very much improved”) or 2 (“Much improved”).

Patients who did not record CGI-I information at any timepoint, or who did not meet the response criteria at any of the assessments, were classed as non-responders.

The numbers of patients (numerators) for these end points are presented below (see the end point above for details of the statistical analysis).

End point type	Secondary

End point timeframe:

This secondary exploratory end point was assessed at 10, 20, 30, 50, 60, 90 and 120 minutes post-Dose 1.

End point values	Inhaled loxapine (FAS)	Aripiprazole (FAS)	Total (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	179	178	357	
Units: Number of patients				
Number of responders (10 min)	25	7	32	
Number of responders (20 min)	53	16	69	

Number of responders (30 min)	76	42	118	
Number of responders (50 min)	102	78	180	
Number of responders (60 min)	124	96	220	
Number of responders (90 min)	136	127	263	
Number of responders (120 min)	141	138	279	
Cumulative number of responders (10 min)	25	7	32	
Cumulative number of responders (20 min)	53	18	71	
Cumulative number of responders (30 min)	77	45	122	
Cumulative number of responders (50 min)	104	81	185	
Cumulative number of responders (60 min)	125	100	225	
Cumulative number of responders (90 min)	144	132	276	
Cumulative number of responders (120 min)	151	147	298	

Statistical analyses

No statistical analyses for this end point

Secondary: The value of the CGI-I score at 10, 20, 30, 50, 60, 90 and 120 minutes following Dose 1 of inhaled loxapine compared with aripiprazole

End point title	The value of the CGI-I score at 10, 20, 30, 50, 60, 90 and 120 minutes following Dose 1 of inhaled loxapine compared with aripiprazole

End point description:

CGI-I scores of 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse.

End point type	Secondary

End point timeframe:

This secondary exploratory end point was assessed at 10, 20, 30, 50, 60, 90, 120, and 1440 minutes post-Dose 1.

End point values	Inhaled loxapine (FAS)	Aripiprazole (FAS)	Total (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	179	178	357	
Units: CGI-I Value				
arithmetic mean (standard deviation)				
10 min	3.47 (± 0.89)	3.81 (± 0.52)	3.64 (± 0.75)	
20 min	2.97 (± 1.06)	3.46 (± 0.77)	3.21 (± 0.96)	
30 min	2.53 (± 1.02)	3.05 (± 0.94)	2.79 (± 1.01)	
50 min	2.25 (± 0.98)	2.63 (± 1.02)	2.44 (± 1.01)	
60 min	2.08 (± 0.97)	2.38 (± 0.94)	2.23 (± 0.96)	
90 min	1.94 (± 0.97)	2.07 (± 0.99)	2.01 (± 0.98)	
120 min	1.88 (± 1.02)	1.90 (± 0.93)	1.89 (± 0.97)	

1440 min	1.83 (± 1.00)	1.87 (± 0.96)	1.85 (± 0.98)	

Statistical analyses

Statistical analysis title	Wilcoxon (Mann-Whitney) Test

Statistical analysis description:

This analysis was performed on the mean CGI-I values for all patients in the FAS using a Wilcoxon rank-sum test (Mann-Whitney).

Comparison groups	Inhaled loxapine (FAS) v Aripiprazole (FAS)
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.492 [3]
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - Mean CGI-I scores were significantly lower with inhaled loxapine vs aripiprazole at 10, 20, and 30 (each p<0.0001), 50 (p=0.0006), and 60 (p=0.0013) minutes post-Dose 1; p=0.1682, p=0.4920, and p=0.4885 at 90, 120 minutes, and 24 hours, respectively.

Secondary: Total number of patients per group who received 1 or 2 doses of study medication with and without rescue medication by 4 hours and 24 hours after Dose 1 or the end of the agitation episode as per the Investigator's judgement, whichever occurred first

End point title	Total number of patients per group who received 1 or 2 doses of study medication with and without rescue medication by 4 hours and 24 hours after Dose 1 or the end of the agitation episode as per the Investigator's judgement, whichever occurred first

End point description:

This end point comprised the:
- Proportion of patients receiving an additional dose of study medication.
- Proportion of patients receiving rescue medication.

The numbers of patients (numerators) for these end points are presented in this end point (see the end point further below for details of the statistical analysis).

End point type	Secondary

End point timeframe:

This secondary exploratory end point was assessed at 4 hours and 24 hours after Dose 1 or the end of the agitation episode as per the Investigator's judgement, whichever occurred first.

End point values	Inhaled loxapine (FAS)	Aripiprazole (FAS)	Total (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	179	178	357[4]	
Units: Number of patients				
Number of patients received Dose 2	12	17	29	
Number of patients received rescue medication	1	0	1	

Notes:

[4] - Note: All patients who received Dose 2 or rescue medication received it within 4 hours of Dose 1.

Statistical analyses

No statistical analyses for this end point

Secondary: Total proportion of patients per group who received 1 or 2 doses of study medication with and without rescue medication by 4 hours and 24 hours after Dose 1 or the end of the agitation episode as per the Investigator's judgement, whichever occurred first

End point title	Total proportion of patients per group who received 1 or 2 doses of study medication with and without rescue medication by 4 hours and 24 hours after Dose 1 or the end of the agitation episode as per the Investigator's judgement, whichever occurred first

End point description:

This end point comprised the:

- Proportion of patients receiving an additional dose of study medication.
- Proportion of patients receiving rescue medication.

The numerators for the percentages are presented in the end point above.

End point type	Secondary

End point timeframe:

This secondary exploratory end point was assessed at 4 hours and 24 hours after Dose 1 or the end of the agitation episode as per the Investigator's judgement, whichever occurred first.

End point values	Inhaled loxapine (FAS)	Aripiprazole (FAS)	Total (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	179	178	357[5]	
Units: % patients				
Percent patients received Dose 2	7	10	8	
Percent patients received rescue medication	1	0	0	

Notes:

[5] - Note: All patients who received Dose 2 or rescue medication received it within 4 hours of Dose 1.

Statistical analyses

Statistical analysis title	Chi-squared Test

Statistical analysis description:

Secondary inferential analyses were performed using two group Chi-squared tests and were exploratory in nature. All statistical tests were applied with a 0.05 two-sided significance level.

Comparison groups	Aripiprazole (FAS) v Inhaled loxapine (FAS)

Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3249 [6]
Method	Chi-squared

Notes:

[6] - The proportions of patients in the inhaled loxapine and aripiprazole groups who received Dose 2 (12 [6.7%] vs 17 [9.6%] patients, respectively; p=0.3249) or rescue medication (1 [0.6%] vs 0 patients; p=0.3180) were not significantly different.

Secondary: Time to Dose 2 (PRN) of study medication and time to rescue medication during the Post-treatment Evaluation Period as compared between groups

End point title	Time to Dose 2 (PRN) of study medication and time to rescue medication during the Post-treatment Evaluation Period as compared between groups

End point description:

These end points included:
- Time to Dose 2: Time from Dose 1 until administration of Dose 2.
- Time to rescue medication: Time from Dose 1 until administration of rescue medication.

The data for the time from Dose 1 until administration of Dose 2 are presented in the table below. Regarding the time to rescue medication, only 1 patient in the inhaled loxapine group received rescue medication. The time from Dose 1 until administration of rescue medication in this patient was 150.0 minutes.

End point type	Secondary

End point timeframe:

These secondary exploratory end points were assessed from the time that Dose 1 was administered to 24 hours after Dose 1 or the end of the agitation episode as per the Investigator's judgement, whichever occurred first.

End point values	Inhaled loxapine (FAS)	Aripiprazole (FAS)	Total (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	179[7]	178[8]	357[9]	
Units: Minutes				
median (confidence interval 95%)	139 (130.7 to 168.2)	150 (142.8 to 179.8)	0 (0 to 0)	

Notes:

[7] - A total of 12 patients took Dose 2 of inhaled loxapine.

[8] - A total of 17 patients took Dose 2 of aripiprazole.

[9] - Total of 29 patients took Dose 2 of study medication.
Median time: 143.0 min
95%CI: 143.6 to 169.1

Attachments (see zip file)	Kaplan-Meier Plot of Time to Dose 2 (FAS)

Statistical analyses

Statistical analysis title	Mantel-Haenszel Test

Statistical analysis description:

The time from Dose 1 to Dose 2 was analysed by means of Kaplan-Meier curves. The treatment groups were compared using the Mantel-Haenszel log-rank test. Patients who received study medication and discharged from the study without receiving Dose 2, were censored at the time of discharge from the study or at the time of receiving rescue medication, whichever occurred sooner.

Comparison groups	Inhaled loxapine (FAS) v Aripiprazole (FAS)

Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
P-value	= 0.3315 [11]
Method	Mantel-Haenszel
Parameter estimate	Hazard ratio (HR)
Point estimate	0.695
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.332
upper limit	1.455

Notes:

[10] - TOTAL FAS TIME FROM DOSE 1 to DOSE 2:
Subjects analyzed = 357
A total of 29 patients took Dose 2 of study medication.
Median time: 143.0 minutes
Confidence interval (95%): 143.6 to 169.1
[11] - There were no statistically significant differences between the inhaled loxapine and aripiprazole groups for the time from Dose 1 to Dose 2 of study medication (p-value of 0.3315); the Hazard Ratio was 0.695, with a 95% CI from 0.332 to 1.455.

Secondary: Proportion of patients satisfied with study treatment (based on Item 14 of the TSQM) as compared between groups

End point title	Proportion of patients satisfied with study treatment (based on Item 14 of the TSQM) as compared between groups

End point description:

This end point comprised:
• Patient satisfaction with the medication by assessment time point: The response to Item 14 of the TSQM at 120 minutes after Dose 1, and at 24 hours after Dose 1 or the end of the agitation episode.

The proportion of satisfied patients (considered satisfied if they reported levels 6 or 7 [very satisfied and extremely satisfied, respectively]) by assessment time point was evaluated.

The numerators for the percentages are presented in the end point below.

End point type	Secondary

End point timeframe:

This exploratory secondary end point was assessed at 120 minutes and 240 minutes after Dose 1.

End point values	Inhaled loxapine (FAS)	Aripiprazole (FAS)	Total (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	179[12]	178[13]	357[14]	
Units: % patients				
120 minutes	46	30	38	
240 minutes	54	36	45	
Early termination	0	0	0	

Notes:

[12] - Denominators were:
176 patients (120 minutes)
173 patients (240 minutes)
3 patients (ET)
[13] - Denominators were:
175 patients (120 minutes)

173 patients (240 minutes)
5 patients (ET)
[14] - Denominators were:
351 patients (120 min)
346 patients (240 min)
8 patients (ET)

Statistical analyses

Statistical analysis title	Chi-Squared Test

Statistical analysis description:

Secondary inferential analyses were performed using two group Chi-squared tests and were exploratory in nature. All statistical tests were applied with a 0.05 two-sided significance level.

Comparison groups	Aripiprazole (FAS) v Inhaled loxapine (FAS)
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0024 [15]
Method	Chi-squared

Notes:

[15] - A significantly greater proportion of patients in the inhaled loxapine vs aripiprazole group were satisfied (very satisfied or extremely satisfied) at 120 min (p=0.0024) and 240 min (p=0.0012) post Dose 1; p=NA at the early termination visit.

Secondary: Number of patients satisfied with study treatment (based on Item 14 of the TSQM) as compared between groups

End point title	Number of patients satisfied with study treatment (based on Item 14 of the TSQM) as compared between groups

End point description:

This end point comprised:

- Patient satisfaction with the medication by assessment time point: The response to Item 14 of the TSQM at 120 minutes after Dose 1, and at 24 hours after Dose 1 or the end of the agitation episode.

The proportion of satisfied patients (considered satisfied if they reported levels 6 or 7 [very satisfied and extremely satisfied, respectively]) by assessment time point is presented above.

The numbers of patients (numerators) for this end point are presented below (see the end point above for details of the statistical analysis).

End point type	Secondary

End point timeframe:

This exploratory secondary end point was assessed at 120 minutes and 240 minutes after Dose 1.

End point values	Inhaled loxapine (FAS)	Aripiprazole (FAS)	Total (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	179	178	357	
Units: Number of patients				
120 minutes	81	53	134	
240 minutes	93	63	156	
Early termination	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were monitored throughout the entire study and recorded for at least 4 hours and for a maximum of 24 hours after Dose 1 of the study medication or until the end of the agitation episode as per the Investigator's judgement, whichever occurred first.

Adverse event reporting additional description:

Each patient had to be carefully monitored for AEs. Investigators asked the patient at each timepoint specified in the Study Flow Chart if they had experienced any untoward effects since the last study timepoint. Patients were monitored for bronchospasm for ≥ 1 hour after Dose 1 and Dose 2 (if Dose 2 was administered).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Inhaled loxapine

Reporting group description:

Patients in the Safety Set who received inhaled loxapine. The Safety Set included all enrolled patients who had taken Dose 1. All safety analyses were performed on the Safety Set. Patients in the Safety Set were categorised based on the actual treatment the patients received, irrespective of the treatment to which they were randomised.

Reporting group title	Aripiprazole

Reporting group description:

Patients in the Safety Set who received arpipiprazole. The Safety Set included all enrolled patients who had taken Dose 1. All safety analyses were performed on the Safety Set. Patients in the Safety Set were categorised based on the actual treatment the patients received, irrespective of the treatment to which they were randomised.

Reporting group title	Total

Reporting group description:

The Safety Set included all enrolled patients who had taken Dose 1. All safety analyses were performed on the Safety Set. Patients in the Safety Set were categorised based on the actual treatment the patients received, irrespective of the treatment to which they were randomised.

Serious adverse events	Inhaled loxapine	Aripiprazole	Total
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 179 (0.56%)	0 / 177 (0.00%)	1 / 356 (0.28%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 179 (0.56%)	0 / 177 (0.00%)	1 / 356 (0.28%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	1 / 179 (0.56%)	0 / 177 (0.00%)	1 / 356 (0.28%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
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	Inhaled loxapine	Aripiprazole	Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 179 (32.40%)	49 / 177 (27.68%)	107 / 356 (30.06%)
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	22 / 179 (12.29%)	0 / 177 (0.00%)	22 / 356 (6.18%)
occurrences (all)	23	0	23
Somnolence			
subjects affected / exposed	26 / 179 (14.53%)	25 / 177 (14.12%)	51 / 356 (14.33%)
occurrences (all)	26	25	51

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 April 2015	The purpose of this global protocol amendment (protocol Version 2.0) was to change the categories for assessing the relationship of any clinical adverse experiences to study medication from Related and Unrelated to Probable, Possible, Unlikely, and Not Related. It was also clarified that: • Suspected Unexpected Serious Adverse Reactions are serious adverse events (SAEs) that were judged by the Investigator or the Sponsor to be possibly or probably related to the study treatment administered and assessed by the Sponsor and/or its delegate as unexpected. • Any SAE that occurred outside of the reporting period, for which there was a reasonable possibility of a study drug relationship in the opinion of the Investigator, had to be reported as soon as the site became aware of the event.
05 August 2015	The purpose of this global protocol amendment (protocol Version 3.0) was to facilitate patient recruitment into the study by: A) Removing the upper limit of agitation severity from the inclusion criterion: Therefore, any patients judged to be clinically agitated at Baseline with a value of ≥ 4 out of the 7 items on the CGI-S could be eligible for inclusion in the study. Previous pivotal clinical studies assessing the safety and efficacy of inhaled loxapine or aripiprazole in acutely agitated patients with schizophrenia or bipolar disorder did not specify an upper limit on agitation severity in the eligibility criteria. The eligibility criteria current at the time of the amendment already addressed certain considerations associated with the removal of the upper limit of agitation severity from the inclusion criterion and so limited the recruitment of patients who were most severely affected in a clinically meaningful manner: 1) patients recruited under the protocol amendment, regardless of the severity of their agitation, were required to have documented adequate consent capacity per the Investigator's judgement and to provide written informed consent (except in Spain); 2) the study was designed to ensure that any patients who were likely to be unable to use the inhalation device were excluded from the study. B) Removing the restriction of the use of injectable depot neuroleptics or long-acting second generation antipsychotics within 1 dose interval prior to study drug administration: This change was feasible as the efficacy and safety of the study drug to treat the acute agitation episode could be assessed in this pragmatic clinical study, regardless of the medication used to treat the underlying condition. Removing this eligibility criterion better reflected the clinical practice and standard of care (SOC) of acutely agitated patients with schizophrenia or bipolar disorder.

15 March 2016	The purpose of this global protocol amendment (protocol Version 4.0) was to facilitate patient recruitment into the study on one hand, and also to better reflect the usual clinical practice by changing the Exclusion Criterion 4. Patients were eligible for the study if they were not treated with benzodiazepines or other hypnotics or oral or short-acting IM antipsychotics within 1 hour prior to study drug administration, whereas the previous protocol version stated a 4-hour time interval. The effect of benzodiazepines or other hypnotics or oral or short-acting IM antipsychotics can be seen quite early after administration and, if patients were still judged to be clinically agitated 1 hour later, they were allowed to be enrolled into the study. This change was feasible as the efficacy and safety of the study drug to treat the acute agitation episode could be assessed in this pragmatic clinical study. Changing this eligibility criterion better reflected the clinical practice and SOC of acutely agitated patients with schizophrenia or bipolar disorder and enabled the enrolment of a subject population that is closer to the patient population in which inhaled loxapine and aripiprazole is being used in clinical practice. Other changes made in this protocol amendment included the extension of the planned duration of the clinical study from up to approximately 11 months to up to approximately 36 months.
21 September 2016	The purpose of this global protocol amendment was to update the statistical analysis methodology. The current trial characteristics (i.e., short time of follow-up and condition under study) would not lead to early study withdrawals. For this reason, the analysis planned initially (i.e., the Mantel-Haenszel log-rank test) would not represent any advantage over other standard methods. Therefore, the purpose of this amendment was to document the use of the Wilcoxon rank-sum test, instead of the Mantel-Haenszel log-rank test, to assess the primary efficacy analysis. Additionally, the original analysis (i.e., the Mantel-Haenszel log-rank test) would also be conducted for sensitivity purposes. The inferential analysis was also conducted using the stratified non-parametric van Elteren test, using modified ridit scores, which is as a direct extension of the Wilcoxon rank-sum test for two samples. Other changes made in this global protocol amendment were to: • Confirm that the assessment of the initial sample size estimation would be based on the interim analysis, Stage 1 data of the primary end point of time to response of CGI-I and would be used as estimates in a calculation of the sample size at one-sided 0.025 alpha level and approximately 90% power • Clarify that there would be no adjustment for multiplicity upon the stated alpha level for this study • Clarify that meaningful time (difference between median aripiprazole time to response and median loxapine time to response) was approximately 30 minutes (interim analysis) • Update some administrative information (change in Medical Monitor, Monitoring Committee constitution, Biostatistician)

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.

The results of the study are applicable to the clinical trial population, which may not be fully representative of the population of patients treated in clinical practice.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28376877