PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	SAFETY AND EFFICACY OF SELF-ADMINISTERED INHALED LOXAPINE (ADASUVE®) IN AGITATED PATIENTS OUTSIDE THE HOSPITAL SETTING: PROTOCOL FOR A PHASE IV, SINGLE-ARM, OPEN-LABEL TRIAL
AUTHORS	Garcia, Fernando; Gil, Emilio; Boldeanu, Anca; Baleeiro, Thaïs

VERSION 1 – REVIEW

REVIEWER	Min Dong Cincinnati Children's Hospital Medical Center, USA
REVIEW RETURNED	06-Dec-2017

GENERAL COMMENTS	This clinical study protocol is overall well developed and well written. I have following minor comments: 1. For data analysis, have the authors considered to analyze any potential association between the incidence of adverse events and age or body size metrics such as body weight? Body mass and age may affect loxapine pharmacokinetics and systemic exposure. 2. For sample size determination, the study planned to enroll 500 patients. However some of the subjects may not have any agitation episodes during the 6 months of follow-up, and therefore may not have been administered with ADASUVE to provide meaningful data. Have the authors considered the percentage of patients who may not have any agitation episodes during the trial? How would it influence the sample size for safety evaluation? 3. In the 1st sentence in section 12.1.4, it should be “All” instead of “Al”. 4. On Page 73, the title of section 13.3 has an extra “H”. 5. On Page 74, “care giver” is preferably to be “caregiver”.

REVIEWER	Scott Zeller, MD University of California, Riverside, USA
REVIEW RETURNED	09-Dec-2017

GENERAL COMMENTS	The study protocol appears comprehensive and well-prepared, with appropriate methods and endpoints, and attention to adverse events. Ethics are addressed satisfactorily. The proposed study could produce very compelling data.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
This clinical study protocol is overall well developed and well written. I have following minor comments:

1. For data analysis, have the authors considered to analyze any potential association between the incidence of adverse events and age or body size metrics such as body weight? Body mass and age may affect loxapine pharmacokinetics and systemic exposure.
We had not considered analyzing this association but we will take note for a post hoc analysis. Thank you very much for your suggestion.

2. For sample size determination, the study planned to enroll 500 patients. However, some of the subjects may not have any agitation episodes during the 6 months of follow-up, and therefore may not have been administered with ADASUVE to provide meaningful data. Have the authors considered the percentage of patients who may not have any agitation episodes during the trial? How would it influence the sample size for safety evaluation?
The study plans to include around 500 patients that have been treated with Adasuve for an agitation episode during a period of six months before the inclusion in the study. As the prevalence of agitation episodes in schizophrenic and bipolar population is quite significant (Garriga et al. Assessment and management of agitation in psychiatry: Expert consensus. World J Biol Psychiatry 2016;17:86-128), it is expected that most of these patients will experience a new episode of agitation within the 6-month period of the study.
Nevertheless, even considering that not all of included patients will experience an agitation episode that deserves the use of Adasuve at home, a lower sample size up to 324 patients is powered enough to detect the expected prevalence of severe respiratory problems. Data of real bronchospasm prevalence observed since the launching of Adasuve (including post marketing and well-controlled studies) is 0%. With a sample size of 324 patients, we will be able to detect that the population prevalence of bronchospasm (upper limit of the 95% CI) is lower than 0.93%.

3. In the 1st sentence in section 12.1.4, it should be “All” instead of “Al”.
This typo has been corrected in the protocol (appendix of the manuscript).

4. On Page 73, the title of section 13.3 has an extra “H”.
We have not found any extra “H” neither in this section nor in other.

5. On Page 74, “care giver” is preferably to be “caregiver”.
This typo has been corrected in the protocol (appendix of the manuscript).

Reviewer: 2
The study protocol appears comprehensive and well-prepared, with appropriate methods and endpoints, and attention to adverse events. Ethics are addressed satisfactorily. The proposed study could produce very compelling data.
Thank you very much for your kind comments.

VERSION 2 – REVIEW

REVIEWER	Min Dong Cincinnati Children's Hospital Medical Center Cincinnati, OH, USA
REVIEW RETURNED	02-Jan-2018

GENERAL COMMENTS	I have no other comments.