Author's response to reviews

Title: Transient paradoxical bronchospasm associated with inhalation of the LAMA AZD9164: analysis of two Phase I, randomised, double-blind, placebo-controlled studies

Authors:

Carin Jorup (carin.jorup@astrazeneca.com)
Thomas Bengtsson (thomas.bengtsson@i-mind.se)
Kerstin Strandgården (kerstin.strandgarden@astrazeneca.com)
Ulf Sjöbring (ulf.sjobring@astrazeneca.com)

Version: 3
Date: 29 November 2013

Author's response to reviews: see over
Dear Celine/ Dr Cornacchia

Thank you for giving us the opportunity for responding to your reviewers comments on our manuscript. Below are details of the changes we have made in response to the various comments.

**Reviewer 1 (G Feldman)**

This MS provides an important safety concern with AZD9164, (paradoxical and unexpected drop in FEV$_1$) that was timely identified in 3 out of 4 subjects with COPD within 5-15 mins after inhalation of AZD9164 via Turbuhaler TM device. Thus it is a very important safety issue to report.

- I would suggest to incorporate this Safety issue into the TITLE of the Presentation...

This suggestion has been implemented.

- 3 COPD patients out of four experienced dyspnoea in addition to the unexpected and significant drop in FEV$_1$, which warrants a discussion on Paradoxical Bronchospasm after medication inhalation, not a novel issue, along with a brief literature review...

A new section has been added to the Discussion in response to these suggestions

- Suggestion to mention aclidinium, glycopyrrolate in addition to indacaterol and also olodaterol, abediterol and umeclidinium as being in late stage development

These suggestions have been implemented.

**Reviewer 2 (E Gil)**

There is lack of clarity about the objective of the studies. While in the abstract and page 5 it is mentioned the studies were designed to determine whether or not the citrate buffer was the cause of the initial drop in FEV$_1$ in prior studies, in Study objectives section (page 7) it only refers to safety, tolerability, PK and PD effects. Also in page 5 it is mentioned that the COPD patients cohort was added to the original GMAD study, therefore it implies the exploration of the FEV$_1$ fall was not the main objective of this study.

The study objectives have been re-addressed and slightly expanded in response to these comments.
Although a fall of 30% in FEV$_1$ was defined as stopping criterion, please provide also an analysis based on fall ≥12% in FEV$_1$, which has been previously used to assess the presence of paradoxical bronchospasm with inhaled drugs.

Unfortunately, the requested analysis is unavailable as all work on this compound has ceased.

Safety evaluation

• There is no consistency on how the description of the adverse event data is provided for the GMAD and JMAD studies:
  § Suggest to always mention how many patients in each study had AEs (like it is reported for the JMAD study).

To bring it more clearly into line with the JMAD study reporting we have added “In the GMAD study” at the start of the sentence “A total of 40 AEs was reported by the 18 healthy subjects who received AZD9164, with 31 AEs reported by the 9 who received placebo.” and inserted additional text to provide more details.

  § Also for JMAD study there is a sentence about intensity (“All AEs were of mild intensity”) but this information is not provided for GMAD study

This information is present in the 2nd para, lines 6 and 7, in the sentence “These were all mild in intensity and occurred only with the highest dose.” However, additional text has also been provided to clarify.

  § A table including all AEs will help to understand why the type of AEs reported, their frequency and if there is dose-dependency (not adequate to base it only on total number of AEs by group).

A table showing AEs determined as causally related to treatment has been added for GMAD, JMAD and the COPD cohort. It was not thought relevant to list all AEs that were not attributable to the study drug.

  § Specify to understand why 31 AEs were reported by 8 subjects in the placebo group in GMAD study, which is quite high compared to the other active groups.

Two subjects who received placebo experienced brief cardiac arrhythmias during the treatment period, one had nausea, vomiting, pyrexia and diarrhoea believed to be due to Calicivirus. Others reported a variety of symptoms including headache, fatigue, discomfort, flatulence, lip ulceration abdominal discomfort, none of which were thought to be related to treatment. The high total number of AEs reported by the placebo group is most likely a chance result.
Effects on FEV$_1$:

While individual data is presented in GMAD study, mean values are provided in JMAD study. Data should be consistently described, not only looking at mean values but also at individual level (i.e. X% subjects with decreases ≥12%, X% decreases ≥20% and 30%).

Mean values have been added to the GMAD study text for consistency with the JMAD reporting. The individual data relates only to the discontinued subject and the subject whose fall in FEV$_1$ was noted recorded correctly at first. Additional data as described are not available as work on this compound has ceased.

In JMAD study it is mentioned that mean initial decrease in FEV1 is dose-dependent, but in the GMAD study it is also important to mention that the highest mean decrease was observed with the high dose.

This comment has been addressed, although the lowest dose of 400 μg caused a larger decrease than the intermediate dose of 1000 μg in GMAD. The largest individual drop in FEV$_1$ did occur with the highest dose, however.

Page 16, 1st last 2 sentences of the 1st paragraph: The information provided is not supported by the data presented in figure 3B.

This has now been corrected, with a better explanation of what is shown in Figures 3 A & B in this section.

Minor essential revisions

These have all been made as directed, including redrawing the graphs using the same symbols for each dose used, with a different line thickness to distinguish the two studies.

The figure numbers have been checked and appear to match the legends.

Discretionary revisions

Glycopyrronium and aclidinium have now been included, along with olodaterol, abediterol and umeclidinium as uLABAs and uLAMA in late development.

In the 3rd paragraph there is information on how duration of action compares to ipratropium. Is there any in vitro or in vivo data in comparison with tiotropium?

The study cited as ref 9 in the manuscript shows that in patients with COPD, AZD9164 had a duration of action directly comparable with tiotropium and effects on FEV1 at 24 h at doses of 400 mg and 1200 mg were superior to those seen with tiotropium 18 mg. Bjermer L, Bengtsson T, Jorup C, Lötvall

Please, clarify if the pre-determined stopping criteria related to lab and ECG significant abnormalities were based on investigator discretion or if they were pre-specified by the sponsor in the study protocol. In the latter case, suggest to describe them.

The stopping criteria were pre-specified by the sponsor and some additional details have added in response to this comment.

Please, clarify how a pre-defined maximal exposure level has been defined as a stopping criteria and when PK data was then available to be able to apply this criterion?

There was an interval between each cohort, during which the PK and all other safety data from the completed cohort were analysed. If the pre-defined exposure level had been reached or any safety issue revealed, the safety committee could determine whether to repeat a dose, test a lower dose or decide whether the study should be terminated.

Please, clarify the overall study discontinuation criterion. When do you refer to ≥2 subjects in AZD with other clinically significant changes in lab or other safety parameter, do you refer other abnormalities different from those mentioned in page 8 or are they the same but if present in 2 subjects then the overall study will be terminated?

This refers to any other abnormalities detected and represents additional safety considerations for the subjects in the study.

In page 17 is describes that the GMAD study was stopper because 3 patients had FEV1 fall greater than 30% in AZD treatment, but in the HS cohorts there were 2 subjects also with FEV1 fall greater than 30% (one in the 400 ug dose and another one in the 2800 ug dose). Why the study was not discontinued at that time?

One of the two healthy subjects with a fall > 30% was unable to exhale adequately for spirometry and was discontinued from the study. His result may have been an artefact resulting from his poor technique and was not regarded as clinically significant. The other fall > 30% was not detected at the time due to a reporting error by the clinical research organisation. It was, however, detected by AstraZeneca when the study data were checked again, retrospectively.

**Study subjects:**

Why female patients were allowed in the COPD cohort but not in the healthy subjects cohort?

Healthy female subjects were allowed, but by chance none were recruited.
Where COPD drugs other than b2-agonists prohibited to be used during the study period by the COPD cohort? Please, clarify this.

Short-acting β₂-agonists and inhaled corticosteroids (ICS) at a stable dose were permitted to be used during the study period by the COPD patients. LAMAs and short-acting muscarinic antagonists (SAMAs) were not permitted. LABAs (alone and in combination ICS) were not permitted. This has been added to the ms.

To clarify the reason why the 3rd cohort in JMAD study was not dosed. I assume it was because of the FEV1 fall observed in COPD patients, but there is no clarity on whether the COPD cohort was dosed after the 1000 ug dose in HS in GMAD study was shown to be safe or when the high dose was dosed and safety was proven. Please, provide information on the chronology of the events until deciding stopping the study.

The COPD cohort was dosed after the highest dose cohort in GMAD and after the 2nd dose in JMAD. As a result of the findings, the planned 3rd cohort in JMAD was never dosed.

Safety evaluation:

Please, clarify if the 11% decrease in FEV1 in the 400 ug dose and the 20% in the 1000 ug dose were reported as AEs (PT: bronchospasm) or were only spirometric findings not considered clinically significant by the investigator and that the only associated AE reported was the cough.

These decreases in FEV₁ were not reported as AEs, but the cough was. Both decreases occurred at 5 min post-inhalation and were transient. Return to baseline FEV₁ occurred by 30 mins for the 400 μg dose and by 2 h for the 1000 μg dose.

Considering the potential effect of anticholinergic drugs on the heart due to the effect on M2 receptors, it would be worth to expand a bit on the heart rate data or QTcF results.

We have added “There were no QTcF values exceeding 450 ms and no notable changes from baseline in QTcF after administration of AZD9164.” to the Safety evaluation section text.

Pharmacokinetics:

Is there any explanation why the plasma levels are higher in COPD patients compared to HS?

The plasma concentrations at 1 hour were higher in COPD patients than in healthy subjects, but the increase was judged to be of minor importance (levels within one doubling dose when dose linearity is assumed) and an explanation would be inappropriate since the concentrations were similar at 24 hour and in total only 3 patients on active treatment were studied.

Discussion:

The 1st paragraph indicated that the COPD patients have a different airway response to AZD than healthy subjects, but in fact, also fall in FEV1 is also observed in healthy subjects.

The text has been amended in response to this comment.