From: [redacted]
To: External Evaluations
Subject: RE: Expert Advice for the Therapeutic Goods Administration [SEC=UNCLASSIFIED]
Date: Tuesday, 28 November 2017 2:40:00 PM
Attachments: image001.png

Dear [redacted]

I realise my advice on this matter is long overdue and I have gone back to this matter a number of times.

Caveat: I must confess that I am not an expert in this specific area (analysis of sequential designs for BE studies) but perhaps I can provide some general advice.

The general approach seems robust to me. I like the fact that the data analysis plan/method outlines the rules for acceptance or rejection. Especially the fact that there is a correction for the statistical limits with each sequence.

I took the opportunity to go back to the cited paper by Potvon et al and this approach is faithfully reflected in the decision tree outlined in your email (extracted form the pivotal study).

See here: http://pqri.org/wp-content/uploads/2015/08/pdf/Potvin_etal_2007.pdf

I also understand that this approach has been accepted by major international regulators. Cited here http://bebac.at/lectures/Moscow2014WS3.pdf

Overall my assessment is that this approach is appropriate

Once again, apologies for the delay.

[redacted]

From: [redacted]@health.gov.au] on behalf of External Evaluations [ExternalEvaluations@health.gov.au]
Sent: Monday, 30 October 2017 2:25 PM
To: [redacted]
Subject: RE: Expert Advice for the Therapeutic Goods Administration [SEC=UNCLASSIFIED]

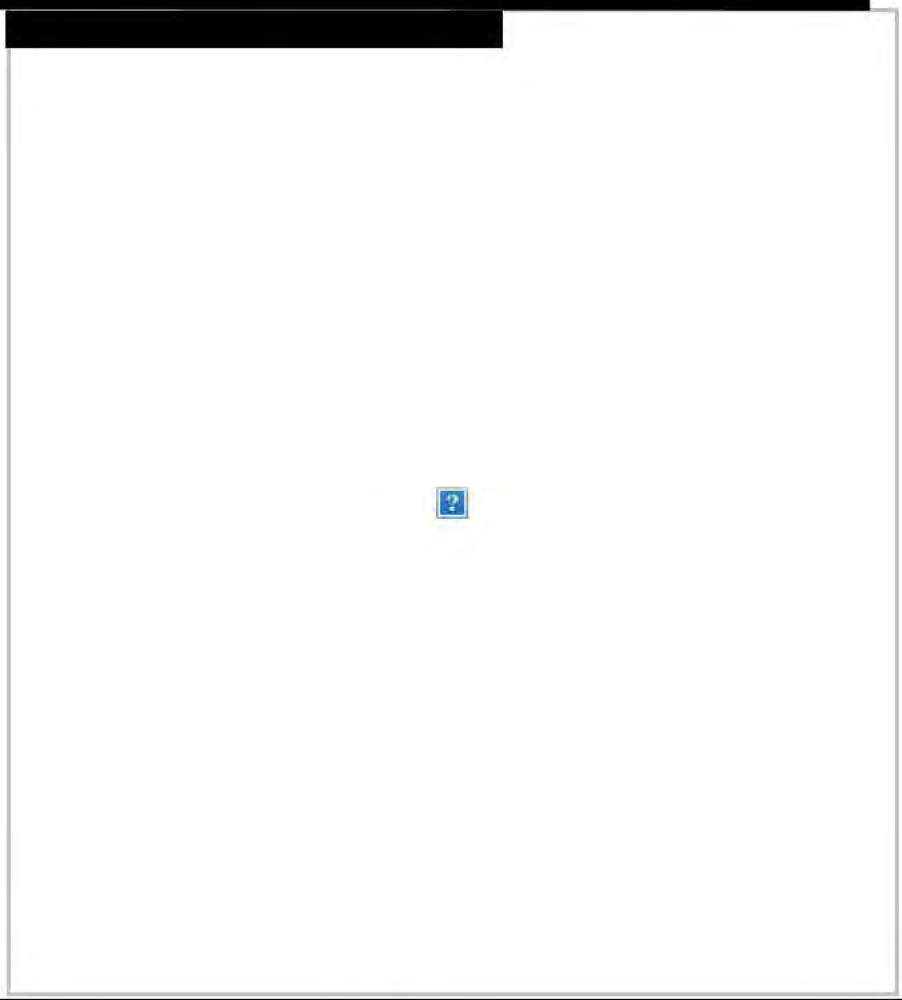
Hi [redacted]

Thank you for agreeing to do this. The Report is due 16th November 2017.
This is the information
Here is the SOR for BRALTUS.

- This submission is to register a Generic Version of SPIRIVA powder for inhalation capsules (AUST R 81525).
- Like the Reference Product the proposed product contains blisters of the formulations product in a delivery device. Each activation opens a blister and allows the contents to be inhaled.
- The amount in the blisters for proposed product is less than in the blisters for SPIRIVA, but the device is different and the delivered dose is claimed to be the same. The TGA will evaluate the *in vitro* data claimed to demonstrate this.
- Following EU Guidance CPMP/EWP/4151/00 Rev 1., therapeutic equivalence is claimed based on bioequivalence to SPIRIVA.
- The submission included three bioequivalence studies (see below), but the pivotal study is CLL13002.

- This study was done is two stages (18 subjects followed by 12; 30 subjects in total). As such, it is the TGAs understanding that the Confidence Intervals (CIs) should be adjusted from 90% at both the interim and final analyses. It looks like this was done for the interim, but not the final (decision tree included below).

[redacted]



[redacted]

  - **Question 2.**
  - **Is the statistical model used valid?**
- If you cannot answer these questions based on the information in the dossiers, please draft questions to put to the sponsor in order to obtain this information.

Study Number	Comments
CLL13002	**Pivotal study.** Randomized, open, three-way, semi-replicate, crossover pharmacokinetic study in a two-stage design for evaluation of the systemic safety of Tiotropium 10 µg delivered dose inhalation powder, hard capsule (Test) compared to SPIRIVA 18 microgram, inhalation powder, hard capsule (10 µg delivered dose) (Reference) each one administered as a single dose of 20 µg delivered dose of tiotropium (2 capsules) in healthy subjects
CLL12003	Randomized, double-blind, double-dummy, three-way, semi-replicate, crossover pharmacokinetic study in a two-stage design for evaluation of the systemic safety of Tiotropium 10 µg delivered dose inhalation powder, hard capsule (Test) compared to SPIRIVA 18 microgram, inhalation powder, hard capsule (10 µg delivered dose) (Reference) each one administered as a single dose in healthy subjects
CLL11002	Pilot study. Open, randomized, three-way crossover study for the evaluation of the bioavailability of

	Tiotropium 12 µg inhalation powder (Laboratorios Liconsa, S.A., Spain) and Tiotropium 18 µg inhalation powder (Laboratorios Liconsa, S.A., Spain) vs. Spiriva 18 microgram inhalation powder, hard capsule, Boehringer Ingelheim International GmbH, Germany in healthy subjects

Kind Regards

[redacted]

From: [redacted]
Sent: Monday, 30 October 2017 1:37 PM
To: External Evaluations
Subject: Re: Expert Advice for the Therapeutic Goods Administration [SEC=UNCLASSIFIED]

[redacted]

Apologies for the delay
Happy to do this review

[redacted]

[redacted]

On 30 Oct 2017, at 12:05 pm, External Evaluations <ExternalEvaluations@health.gov.au> wrote:

> Hi [redacted]
> Just chasing up if you are interested in providing Expert Advice as per my email below
> Kind Regards
>
> [redacted]
>
> ---
>
> **From:** [redacted]@health.gov.au] **On Behalf Of** External Evaluations
> **Sent:** Thursday, 19 October 2017 10:35 AM
> **Subject:** FW: Expert Advice for the Therapeutic Goods Administration [SEC=UNCLASSIFIED]
>
> Good Morning [redacted]
> The purpose of this email is to inquire about your availability to provide expert advice to the TGA on a pharmaceutical; proposed for registration in Australia.
> The proposed indication for the pharmaceutical lies within your area of specialist clinical expertise.
> We do not require a complete evaluation of the sponsor's clinical dossier. The clinical dossier has already been evaluated; we now need expert advice on a particular issue or a narrow range of issues.
>
> The Advice would be due **16th November 2017**
> Because submissions to the TGA are commercial in confidence we cannot provide specific details of the request at this preliminary stage. Consequently, the process involves two steps:
> * We would firstly ask you to sign a conflict of Interest and confidentiality agreement (see attached) and return it to the TGA via return email.
> * We will provide you with preliminary details of the particular issue or narrow range of issues; if you are still interested and available, we would then provide complete details and negotiate a timeline.
> Any advice you provide to the TGA will also be provided to the sponsor (pharmaceutical company). Your identity will remain confidential.
> We may also need you to comment (at a later stage) on the sponsor's response to your advice.
> **The Delegate is** [redacted] **who can be reached on** [redacted]
>
> - **Active Ingredient:** Tiotropium (as Bromide)BRALTUS
> - **Sponsor:** Teva Pharma Australia Pty Ltd

- **Proposed Indication:** BRALTUS is contraindicated in patients with a history of hypersensitivity to tiotropium bromide, atropine or its derivatives, e.g. ipratropium or oxitropium or to any other component of this product

If you require further information please do hesitate to contact me

If you require further information please do hesitate to contact me

Kind Regards

Kind Regards

[redacted]
[redacted]
Evaluation Management
Prescription Medicines Authorisation Branch
[redacted]
Email: ExternalEvaluations@health.gov.au
Therapeutic Goods Administration
Department of Health
PO Box 100
Woden ACT 2606 Australia
www.tga.gov.au

This response is general information given to you without prejudice; it is not binding on the TGA and you should get your own independent legal advice to ensure that all of the legislative requirements are met.

"Important: This transmission is intended only for the use of the addressee and may contain confidential or legally privileged information. If you are not the intended recipient, you are notified that any use or dissemination of this communication is strictly prohibited. If you receive this transmission in error please notify the author immediately and delete all copies of this transmission."