CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210595Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 72252

MEETING PRELIMINARY COMMENTS

AstaraZeneca Pharmaceuticals LP
One MedImmune Way
Gaithersburg, MD 20878

Attention: Steve Danielson
Senior Director, Global Regulatory Affairs

Dear Mr. Danielson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Aclidinium Bromide and Formoterol Fumarate.

We also refer to your September 15, 2017, correspondence, received September 15, 2017, requesting a meeting to discuss the acceptability of the content and form of your future NDA submission.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me, Regulatory Project Manager at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Sadaf Nabavian, Pharm.D.
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: November 28, 2017; 3:00-4:00 p.m. EST
Meeting Location: White Oak Building 22, Conference Room: 1415

Application Number: IND 72252
Product Name: Aclidinium Bromide and Formoterol Fumarate (AB/FF)

Indication: Chronic Obstructive Pulmonary Disease (COPD)
Sponsor: AstaraZeneca Pharmaceuticals LP

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 28, 2017, at 3:00 p.m., Building 22, Conference Room 1415, between AstaraZeneca Pharmaceuticals LP, and the Division of Pulmonary, Allergy, and Rheumatology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

The purpose of the meeting is to discuss the acceptability of the content and format in support of a future registration for Aclidinium Bromide and Formoterol Fumarate Fixed Dose Combination (FDC), Dry Powder Inhaler (DPI), for the indication of Chronic Obstructive Pulmonary Disease (COPD). AstraZeneca Pharmaceuticals LP submitted a request for a meeting on September 15, 2017, to the Division of Pulmonary, Allergy, and Rheumatology Products, and the Division granted the meeting on October 6, 2017. The briefing package was submitted on October 24, 2017.

2.0 DISCUSSION

Question 1:

Reference is made to the 2013 pre-NDA meeting (Reference ID 3366055), in which the Division agreed that the completed nonclinical program is adequate to support the filing of an NDA. Does the Division still agree?

FDA Response

Your nonclinical program is adequate to support the filing of an NDA.

Provide a safety assessment of extractables and leachables for all primary container closure components of the device that are in contact with the drug product during storage as well as secondary container closure components where there is a potential for migration of leachables into the drug product. Refer to USP Chapters 1663 and 1664 for the design of extractables and leachables studies, respectively.

Question 2:

The investigational product for the Phase III trials was produced at (b) (4) ***. The same manufacturing equipment is currently installed at AstraZeneca AB, Sweden Operations, Gärtunavägen. The same process will be run on this equipment, and ICH site-specific stability batches will be produced at this site. AstraZeneca intends to include both sites as drug product manufacturers in the NDA. Does the Division agree that the proposed in vitro package will appropriately confirm comparability between AstraZeneca AB and*** (b) (4) ***?***

FDA Response

Your approach to obtain and compare dose content uniformity (DCU) and aerodynamic particle size distribution (APSD) data to assess any impact due to the different manufacturing sites appears to be reasonable, however, it is premature to agree to any particular degree of comparability in the absence of the data. In making a determination of comparability across the sites, we will need to consider, in consultation with the clinical team, differences in the data means, data variability (within units, between units, between batches), trends in the data, with time, and the particular drug substance involved. We will examine and compare other stability parameters as well.

Question 3:

Does the Division agree with the proposed specification for α-lactose monohydrate?

FDA Response

Your approach to use your prior knowledge with lactose from Tudorza production to develop the specification for the AB/FF FDC DPI product is reasonable. Provide your proposals for the lactose test parameters that are omitted relative to the approved Tudorza lactose specification, with supportive data and justification, in Section P.4.4, of your future NDA submission.

Question 4:

Does the Division agree with the proposed drug product NDA specification, specifically with the proposal for testing beginning and end actuations, only, for FPD and groupings?

FDA Response

We agree with the test parameters that you plan on including in the drug product specification, except that we note that you do not plan to include a test for (b) (4) Provide justification, with supporting data, for the absence of such testing in Section P.5.6, of your future NDA submission. It is premature to agree to the specific acceptance criteria proposed prior to our review of your application. Regarding the (b) (4) testing, it is generally acceptable to test (b) (4)

Question 5:

AstraZeneca acknowledges the feedback provided by the Division at the 2013 pre-NDA meeting (Reference ID 3366055) and subsequent interactions (Type C written response [Reference ID 3462480], Type C meeting [Reference ID 3606418]). The in vitro data presented in the briefing book for the batches used in the Phase III Study D6571C00001 confirm the comparability of the delivered dose and (b) (4) ***of the monotherapy- and combination formulations. Does the Division agree?***

FDA Response

We agree that there is sufficient comparability of the in vitro dose delivery performance when comparing the AB/FF FDC DPI to the two monotherapy drug products. The differences noted are not expected to confound the interpretation of the clinical trial data.

Question 6:

Study D6571C00001 has confirmed the bronchodilatory effects observed in the previous studies (M/40464/30 and LAC-MD-31), demonstrating the clinical benefits of the combination of AB/FF over FF and AB monotherapy as assessed by trough FEV1 and FEV1 at 1 hour post-dose administration, respectively. The efficacy data package from the complete Phase III

Program (D6571C00001, M/40464/30, and LAC-MD-31) supports an NDA filing of AB/FF 400/12µg BID for the maintenance treatment of COPD. Does the Division agree?

FDA Response

Yes, we agree. The proposed efficacy data package would support filing and review of your future NDA. Note that in the assessment of efficacy, we will consider the primary spirometric endpoints (1-hour post-dose FEV1 and trough FEV1), as well as other spirometric parameters (e.g., FEV1 curves). Additionally, clinically relevant endpoints (e.g., SGRQ, COPD exacerbation) will also be considered in determining efficacy.

Question 7:

AstraZeneca acknowledges the Division's feedback regarding the appropriate dose of FF in combination with AB (2013 pre-NDA meeting [Reference ID 3366055], 2014 Type C interactions [Reference IDs 3462480 and 3606418], and 2015 Type C interactions and comments [Reference IDs 3817871, 3849884, and 3861362]). Study D6571C00002, designed in accordance with the Division's feedback, has demonstrated that the pharmacodynamic bronchodilator effect of FF 12 µg delivered via PRESSAIR after multiple doses (Day 7), is closer to that of PERFOROMIST 20 µg than either the FF 6 µg or 24 µg doses delivered via PRESSAIR, and therefore FF 12 µg is the optimal dose for the AB/FF fixed-dose combination product. Does the Division agree?

FDA Response

Based on the summary data in the meeting package, the proposed dose of FF in the AB/FF fixed combination appears reasonable. However, this will be a review issue.

Question 8:

Along with the individual study analyses, efficacy data from the pivotal Phase III studies (D6571C00001, LAC-MD-31, and M/40646/30) will be integrated for the main spirometric endpoints, health-related QOL, and exacerbation endpoints, to provide a more precise estimate of the treatment benefits of AB/FF 400/12 µg and to evaluate consistency of effects across subgroups of demographic and other baseline characteristics. Does the Division agree with the proposed strategy for pooling data from completed Phase III studies to support the integrated summary of efficacy (ISE)?

FDA Response

Pooled efficacy analyses are at your discretion. In our review, the assessment of efficacy will consider each trial individually.

Question 9:

Does the Division agree that the proposed safety data package supports an NDA submission for AB/FF 400/12 µg as a maintenance treatment (b) (4) ***in patients with COPD*** (b) (4) ***?***

FDA Response

Yes, we agree. The proposed safety data package is sufficient to support review. Pending review, the size of the safety database appears be adequate.

Question 10:

The primary analysis of the safety profile of AB/FF BID will be performed on the pooled population from Phase III studies with at least 6 months of duration that are placebo-controlled (M/40464/30 and LAC-MD-31/36). Supportive evidence will be provided by analyses of pooled data from the patient population of the above-mentioned clinical studies plus all additional Phase III studies of at least 6 months of duration that are active comparator-controlled (LAC-MD-32, D6571C00001, M/40464/39). A secondary source of safety data will be provided by the short-term Phase I/II studies, which will be presented individually. Does the Agency agree that this proposal is acceptable for the assessment of the safety profile in the Integrated Summary of Safety (ISS)?

FDA Response

Your proposed approach appears reasonable. However, also include a pooled analysis of the 6-month placebo controlled trials M/40464/30 and LAC-MD-31 only, as well as a separate analysis of the 52-week trials.

Question 11:

The Sponsor plans to provide a letter authorizing FDA to refer to AstraZeneca's TUDORZA® PRESSAIR® (AB) Inhalation Powder NDA 202-450 and SYMBICORT® MDI (budesonide/FF) Inhalation Aerosol NDA 21-929 in support of the upcoming NDA submission. Does the Division agree that these letters of cross-reference will support the AB and FF monocomponents, respectively, in particular for the nonclinical studies and clinical pharmacology (ie, human biomaterial studies), as well as extensive clinical safety data, conducted under NDAs 202-450 and 21-929 and that no further cross-reference to other products is necessary?

FDA Response

Yes, your approach appears reasonable.

Question 12:

In accordance with FDA's Guidance for Industry, "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document," AstraZeneca proposes to place the text portion of the ISE and ISS within Module 2 as the Summary of Clinical Efficacy and Summary of Clinical Safety, Sections 2.7.3, and 2.7.4, respectively. The tables, figures, appendices, data sets, and analysis programs will be placed in Section 5.3.5.3. Does the Division agree?

FDA Response

Yes, your proposal is acceptable.

Question 13:

A Study Data Standardization Plan was submitted to IND 72,252 on 11 September 2017. Does the Division agree with the structure and the content of the Study Data Standardization Plan?

FDA Response

Yes, we agree.

Question 14:

Patient profiles will not be included in the NDA because all collected subject data will be included in SDTM datasets. Does the Division agree?

FDA Response

Yes, we agree.

Question 15:

Clinical trials were conducted in Japan to support a marketing application for AB/FF with the Pharmaceuticals and Medical Devices Agency. The Sponsor will include these final clinical study reports in Module 5 of the NDA submission. These studies will not be pooled and the Sponsor does not intend to submit the Japanese databases, which are in Japanese, with the NDA submission. Does the Division agree?

FDA Response

Yes, we agree. The Japanese clinical study reports should be presented in English.

Question 16:

The Sponsor intends to follow the December 2012 draft guidance regarding Summary Level Clinical Site Data for the Center for Drug Evaluation and Research's (CDER's) Inspection Planning (BIMO\OSI requirements). The Sponsor will submit this package for the following Phase III studies: Studies M/40464/30, LAC-MD-31, LAC-MD-36, LAC-MD-32, and Study D6571C00001 only. Does the Division agree that the identified studies are sufficient for the BIMO\OSI package?

FDA Response

Yes, we agree. Submit clinical site level datasets (for the BIMO inspection site selection tool), for the five Phase 3 studies that you identified (Studies M/40464/30, LAC-MD-31, LAC-MD-36, LAC-MD-32, and LAC-MD-37).

Question 17:

This Briefing Package provides the table of contents for the planned eCTD (electronic common technical document) submission and information on how studies will be organized. Does the Division agree with the organization of the eCTD as outlined?

FDA Response***:***

Yes, your proposed organization of the eCTD appears acceptable.

Additional Comments:
We understand that you are planning to use aclidinium bromide/formoterol fumarate to treat (b) (4) patients with chronic obstructive pulmonary disease (COPD) (b) (4) . However, you have not submitted a comprehensive risk analysis or your plans for a Human Factors (HF) validation study.

We recommend you conduct a comprehensive use-related risk analysis if you have not already completed one. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures.

If models of the same or similar combination products exist, your use-related risk analysis should incorporate applicable information on known use-related problems with those products. Useful information can be obtained from your own experience as well as from public sources such as

literature, adverse event reports, and product safety communications (see draft guidance for industry Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development).

Additionally, if models of the same or similar combination products exist, it may be useful to conduct comparative analyses such as a labeling comparison, a comparative task analysis, and a physical comparison between your proposed product and the comparator for the purposes of identifying what differences exist between the user interfaces and where the same or similar risks may apply to your proposed product.

Based on the aforementioned information and data, you should determine whether you need to perform a human factors (HF) validation study. If you determine that an HF validation study is not needed for your product, submit your risk analysis, comparative analyses, and justification for not conducting the HF validation study to the Agency for review under the IND. We will notify you if we concur with your determination.

3.0

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation

conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

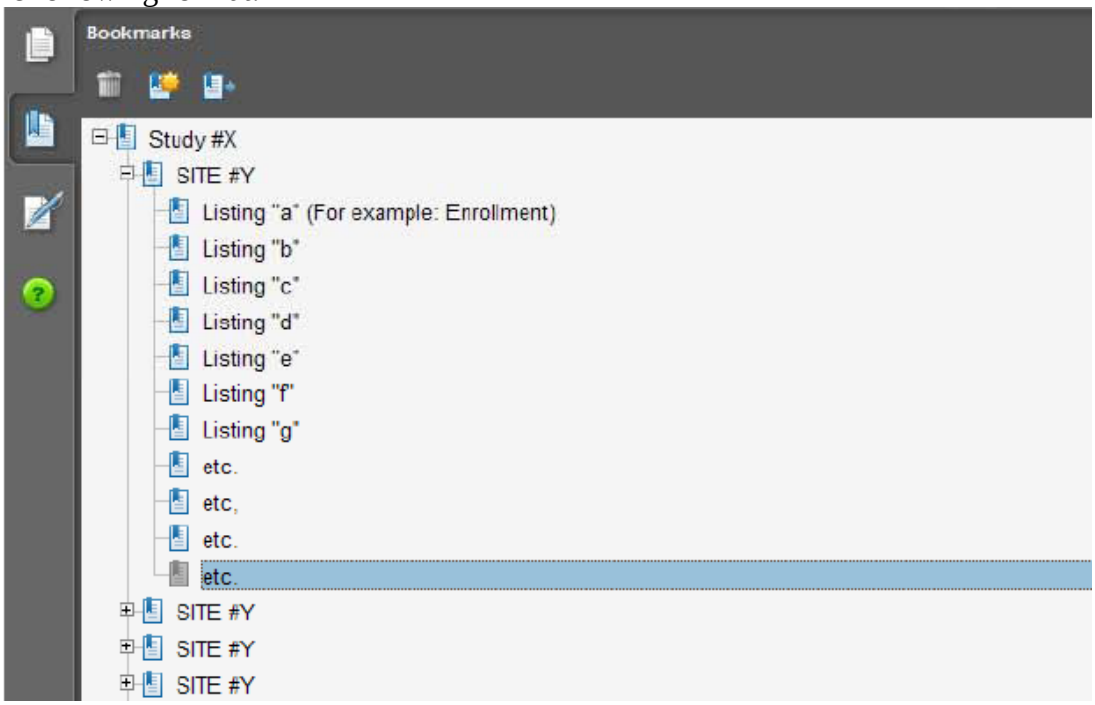
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SADAF NABAVIAN
11/21/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 72252

**MEETING REQUEST-
WRITTEN RESPONSES**

AstraZeneca Pharmaceuticals, LP
One MedImmune Way
Gaithersburg, MD 20878

Attention: Annie Foster
Regulatory Affairs Director

Dear Ms. Foster:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Aclidinium Bromide and Formoterol Fumarate Fixed Dose Combination Inhaler.

We also refer to your submission dated June 24, 2015, received June 30, 2015, containing a Type C meeting request. The purpose of the requested meeting was to obtain agreement on two proposed study designs in support of a future registration for your product.

Further reference is made to our Meeting Granted letter dated July 20, 2015, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your August 7, 2015, background package.

If you have any questions, call me, Senior Regulatory Project Manager at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Sadaf Nabavian, Pharm.D.
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type:	C
Meeting Category:	Guidance
Application Number:	IND 72252
Product Name:	Aclidinium Bromide and Formoterol Fumarate DPI
Indication:	COPD
Sponsor:	AstraZeneca Pharmaceuticals, LP
Regulatory Pathway:	505(b)(2)

1.0 BACKGROUND

This document provides written responses to AstraZeneca's questions on two proposed study designs in support of a future registration for aclidinium bromide and formoterol fumarate DPI. The Division granted the meeting as written responses and the background materials were received by the Agency on August 7, 2015.

2.0 QUESTIONS AND RESPONSES

Question 1:

Does the Agency agree that the proposed 6 month Phase 3 study (LAC37) to assess the contributions of formoterol and aclidinium using the same co-primary endpoints as for completed Phase 3 studies M/40464/30 and LAC-MD-31 (i.e., change from baseline to Week 24 in 1 hour post-dose FEV_1 and morning pre-dose [trough] FEV_1, respectively) in the same target patient population will be adequate to support a future NDA filing for the aclidinium/formoterol FDC?

FDA Response:

We agree with the co-primary endpoints and target patient population for proposed study LAC37. However, we disagree with the inclusion of a placebo comparator group in this study. Aclidinium as a monotherapy already has been approved for the proposed indication; your formulation of formoterol was shown to be superior to placebo in Studies 30 and 31 Pre-NDA meeting package on July 5, 2013. Given these results and the primary goal of demonstrating the contribution of aclidinium to the combination, it is ethically unjustified to have patients with moderate to severe COPD on placebo for the 6-month duration of this study.

Question 2:

Does the Agency agree with the proposed method to adjust tests of the primary and secondary endpoints for multiplicity within the proposed 6 month Phase 3 study (LAC37)?

FDA Response:

We agree with your general approach to multiplicity control. However, we refer you to our response to Question 1.You may update your testing hierarchy accordingly.

Question 3:

To facilitate cross-study comparisons, AstraZeneca proposes the use of a mixed-model repeated measures (MMRM) method for handling of missing data in study LAC37 to parallel the completed studies LAC-MD-31 and M/40464/30. Does the Agency agree with AstraZeneca's proposals?

FDA Response:

Your proposed MMRM and sensitivity analyses are appropriate given that subjects who discontinue treatment will be followed for efficacy assessments. The only reason for withdrawal from study should be a subject's withdrawal of consent. We recommend that the informed consent form includes a statement informing patients about the continued scientific importance of their data even if they discontinue study therapy. Your sensitivity analyses also should include "tipping point" multiple imputation analyses that include the possibility that patients on the combination product have worse outcomes than patients on monotherapies.

Question 4:

In July 2014, FDA recommended extending proposed Phase 3 study LAC37 from 3 months to 6 months duration to allow assessment of numerical trends in reduction in rates of exacerbation. Exacerbation trends will be examined by comparing aclidinium/formoterol 400/12 µg with each monotherapy (aclidinium 400 µg and formoterol 12 µg). Does the Agency agree with the proposed method for examining this trend, defined as a risk ratio <1 comparing the combination to the monotherapies?

FDA Response:

Assuming that the parameters utilized in your power calculation are correct, the proposed method is acceptable.

Question 5:

The completed aclidinium/formoterol FDC Phase 3 studies included 2208 patients from North America (55.4% of a total Phase 3 population of 3986). Of the total Phase 3 population of 1111 exposed to aclidinium/formoterol 400/12 µg to date, 716 subjects (64.5%) were North American. Does the Agency agree that recruitment of approximately 50% of the patients in study LAC37 from North America will be adequate?

FDA Response:

Your proposal is acceptable.

Question 6:

Does the Agency agree with the sponsor's proposal to utilize efficacy data from completed studies LAC-MD-31 and M/40464/30 and the proposed new Phase 3 study LAC37 to support a future NDA filing, provided the clinical benefits of formoterol in combination with aclidinium over aclidinium monotherapy are demonstrated in study LAC37?

FDA Response:

Pending review of the results of Study LAC37, your plan is acceptable.

Question 7:

Study LAC-MD-31 has demonstrated a clinically and statistically significant improvement in quality of life as assessed by SGRQ total score of aclidinium/formoterol 400/12 µg compared to placebo (–4.4; p=0.0008 after multiplicity adjustment). If study LAC37 also shows statistically and clinically significant improvement in SGRQ total score (i.e., ≥4 units vs. placebo), does the Division agree with the sponsor's proposal to use results from both studies (LAC-MD-31 and LAC37) to support a label claim on SGRQ in the clinical trials section of the prescribing information?

FDA Response:

We agree that SGRQ will be included in the clinical trials section of the prescribing information. SGRQ results should be analyzed using responder analysis where a responder is defined as improvement of at least 4. The responder analysis of SGRQ should compare the combination therapy to each of the individual monotherapies.

Question 8:

As in completed Phase 3 studies M/40464/30 and LAC-MD-31, subjects in study LAC37 will complete the 14 question EXACT questionnaire daily. However whereas the total score of the subset of 11 questions that comprise the E-RS was explored only as an additional endpoint in

M/40464/30 and LAC-MD-31, AstraZeneca would like to focus on the change from baseline in E-RS total score results over 24 weeks as a secondary endpoint in LAC37. These results will provide additional data for the continued use and future qualification of the E-RS assessment tool. Does the FDA agree with the overall approach for the continued use of the E-RS tool in study LAC37?

FDA Response:

Measures derived from The Exacerbations of Chronic Pulmonary Disease Tool Patient Reported Outcome (EXACT-PRO), such as the EXACT-Respiratory Symptoms (E-RS), are best used as exploratory endpoints at this time. Evaluation of the E-RS would not appear in the label. In general, patient reported symptom questionnaires are not reliable for studies of patient populations with moderate to severe disease. While inclusion of the E-RS as an additional endpoint in phase 3 trials is at your discretion, if it is included, you should take steps to ensure that the results of any other symptom questionnaires are not confounded by order of administration and/or concomitant administration of multiple questionnaires.

Question 9:

The sponsor intends to conduct 24 hour serial assessments on Day 1 and at Week 24 (end of treatment) in a subset of 30% of patients in study LAC37 to characterize the bronchodilation profile over that period. Does the Agency agree that the 24 hour FEV_1 curve assessed in a subset of patients in study LAC37 could be included in the clinical trial section of the prescribing information?

FDA Response:

Yes, we agree.

Question 10:

The exacerbation definition used in the Phase 3 aclidinium/formoterol program to date and in the proposed study LAC37 (i.e., a worsening of COPD symptoms for at least two consecutive days requiring a change in COPD treatment [moderate exacerbation: requiring use of antibiotics and/or systemic corticosteroids; severe exacerbation: requiring hospitalization or overnight stay, or resulting in death]) is in line with the exacerbation definition used in the Tudorza Pressair development program. Does the Agency agree that assessments of exacerbations as defined above may be used to support exacerbation claims for aclidinium and/or aclidinium/formoterol?

FDA Response:

Your definition of exacerbation is acceptable.

Question 11:

Does the Agency agree that the proposed design of study LAC28, including the study population (COPD patients with FEV_1 increase of 12% and 200 mL after 400 µg albuterol), treatment duration (1 week), and primary endpoint ($AUC_{0-12/12h}$) will enable selection of the optimal formoterol dose to be combined with aclidinium in Pressair® to address FDA concerns?

FDA Response:

Your approach is acceptable.

Question 12:

Study LAC-PK-01 results show plasma exposures of formoterol 12 µg administered via Pressair® comparable to those obtained with Foradil 12 µg Aerolizer®. In study LAC28, the sponsor anticipates that a 12 µg formoterol dose administered via Pressair® will provide similar efficacy to that of Foradil 12 µg. Does the Agency agree that if the pharmacodynamic profile for formoterol 12 µg in Pressair® is similar to that of Foradil 12 µg Aerolizer® and numerically lower to that of Foradil 2 x 12 µg (24 µg), then the formoterol dose of 12 µg in Pressair® can be accepted as the optimal formoterol dose for the aclidinium/formoterol combination?

FDA Response:

In the meeting package, you use the comparable FF PK exposure via Pressair or Foradil Aerolizer in study LAK-PK-01 as supportive evidence for FF dose selection. Note that systemic exposures from PK studies are only informative for systemic safety profile, and cannot be used to infer efficacy or local effect/safety profile. The PK comparison cannot be used as pivotal evidence to guide dose selection for inhalation products.

3.0

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant

endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of

safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were

approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SADAF NABAVIAN
09/10/2015