

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761180Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

BLA 761180

MEETING PRELIMINARY COMMENTS

LEO Pharma A/S
c/o LEO Pharma Inc.
Attention: Encarnacion Suarez, PharmD
Senior Director, US Regulatory Affairs
7 Girlada Farms, 2nd Floor
Madison, NJ 07940

Dear Dr. Suarez:¹

Please refer to your biologic license application (BLA) submitted under section 351(a) of the Public Health Service Act for tralokinumab injection, 150 mg/ML.

We also refer to your correspondence, dated and received May 7, 2021, requesting a meeting to discuss the deficiencies cited in the April 23, 2021 Complete Response correspondence and the Agency's expectations for a complete BLA resubmission in order to support review and approval.

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.

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

If you have any questions, call me at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Strother D. Dixon
Senior Regulatory Project Manager
Division of Regulatory Operations for
Division of Dermatology and Dentistry
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



PRELIMINARY MEETING COMMENTS

1
2 **Meeting Type:** A
3 **Meeting Category:** Guidance
4
5 **Meeting Date and Time:** June 9, 2021; 9:30 – 10:30 AM EDT
6 **Meeting Location:** teleconference
7
8 **Application Number:** BLA 761180
9 **Product Name:** tralokinumab injection, 150 mg/ML
10 **Proposed Indication:** for the treatment of moderate-to-severe atopic dermatitis in
11 adult patients whose disease is not adequately controlled
12 with topical prescription therapies or when those therapies
13 are not advisable
14
15 **Applicant Name:** LEO Pharma A/S
16 **Regulatory Pathway:** 351(a) of the Public Health Service Act
17
18

Introduction:

19
20 This material consists of our preliminary responses to your questions and any
21 additional comments in preparation for the discussion at the meeting scheduled for
22 June 9, 2021; 9:30 – 10:30 AM EDT, via teleconference between LEO Pharma A/S
23 and the Division of Dermatology and Dentistry. We are sharing this material to
24 promote a collaborative and successful discussion at the meeting. The meeting
25 minutes will reflect agreements, important issues, and any action items discussed
26 during the meeting and may not be identical to these preliminary comments
27 following substantive discussion at the meeting. If you determine that discussion is
28 needed for only some of the original questions, you have the option of reducing the
29 agenda. Contact the Regulatory Project Manager (RPM) if there are any major
30 changes to your development plan, the purpose of the meeting, or the questions
31 based on our preliminary responses, as we may not be prepared to discuss or
32 reach agreement on such changes at the meeting.
33

1.0 BACKGROUND

Purpose:

34
35
36
37 The purpose of the meeting is to discuss the deficiencies cited in the April 23, 2021
38 Complete Response correspondence and the Agency's expectations for a complete
39 BLA resubmission in order to support review and approval.
40

Coronavirus 19 (COVID-19) Clinical Trial Guidance

41
42 During the COVID-19 pandemic, ensuring the safety of trial participants is paramount.
43 Sponsors should consider each circumstance, focus on the potential impact on the
44 safety of trial participants, and modify study conduct accordingly. It is critical that trial

45 participants are kept informed of changes to the study and monitoring plans that could
46 impact them, and that the Agency is appropriately informed of these changes. Refer to
47 the *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19*
48 *Public Health Emergency*. We update guidances periodically. For the
49 most recent version of a guidance, check the FDA Guidance Documents
50 Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

51

52 **Regulatory Correspondence History**

53

54 We have had the following meetings with you.

- 55 • January 27, 2021 – Late Cycle
- 56 • October 7, 2020 – Mid-Cycle

57

58 We have sent the following correspondences:

- 59 • May 19, 2021 – Proprietary Name – Authorization Request
- 60 • May 19, 2021 – Proprietary Name Request Unacceptable
- 61 • April 23, 2021 – Complete Response
- 62 • February 11, 2021 – Discipline Review
- 63 • December 11, 2020 – Information Request
- 64 • November 18, 2020 – Information Request
- 65 • October 21, 2020 – Information Request
- 66 • October 2, 2020 – Information Request
- 67 • September 10, 2020 – Information Request
- 68 • August 26, 2020 – Information Request
- 69 • July 2, 2020 – Proprietary Name Request Conditionally Acceptable
- 70 • July 1, 2020 – Filing Communication – No Filing Review Issues Identified
- 71 • June 1, 2020 – Advice

72

73

74 **2.0 DISCUSSION**

75

76 **2.1. Chemistry, Manufacturing, and Controls**

77

78 **Question 1:**

79 To help LEO Pharma adequately address the deficiency cited in the CRL, can the
80 FDA provide additional background regarding the postmarket information that
81 prompted FDA's request for testing?

82

83 **FDA Response to Question 1:**

84 There is a history of malfunctions associated with this product as demonstrated by
85 120 medical device reporting since 2020, multiple Biological Product Deviation
86 Reports and complaints from industry healthcare professional interest groups. Given
87 this information, the FDA believes there is a high level of risk of needle sticks and
88 the potential for bloodborne pathogen contamination. The preconditioning testing

89 seeks to provide the worst case scenario to test for the high level risk. The testing
90 we recommend recognizes that it is entirely possible, in fact probable, to have aged
91 devices shipped and dropped in some way before use. This combined with a high
92 degree of reliability ensures adequate performance of the device.

93

94 **Question 2:**

95 Does the FDA agree that the test method (compressive override force) and
96 associated statistical approaches (i.e., sample size and k-values) reported in the
97 March 1 and 5, 2021 amendments are adequate to demonstrate needle safety
98 performance as requested in the CRL?

99

100 **FDA Response to Question 2:**

101 [REDACTED] (b) (4)

102 [REDACTED] (b) (4)

103 (b) (4) You may submit data in an annual report if you want to
104 extend your shelf-life to 36 months. The reliability indicated in the Performance
105 report in seq 0033 is not adequate for Needle Safety Activation. As was mentioned
106 in the March 2, 2021 communication, we requested: 1) needle safety override force;
107 and 2) needle safety activation force testing after preconditioning over the shelf-life.
108 Therefore, Needle Safety Activation Force performance after preconditioning over
109 the proposed shelf-life remains unresolved and needs to be provided to ensure
110 reliable deployment of the feature.

111

112 **Question 3:**

113 Does the FDA agree that the methods used to perform drop and simulated shipping
114 are acceptable and meet the requirements for sequential preconditioning as
115 requested in the CRL?

116

117 **FDA Response to Question 3:**

118 The FDA agrees that the methods for drop and simulated shipping were acceptable
119 for Needle Override Force testing. However, the drop and simulated shipping
120 methods need to be applied to Needle Safety Activation force testing using the
121 appropriate reliability (95% confidence, 99% reliability). Malfunction of the Needle
122 Safety Activation may lead to accidental needle stick and subsequent transmission
123 of bloodborne pathogens. Therefore, we believe the proposed reliability and
124 preconditioning is applicable to Needle Safety Activation force performance
125 verification testing. As was mentioned in the March 2, 2021 communication, we
126 requested: 1) needle safety override force; and 2) needle safety activation force
127 testing after preconditioning over the shelf-life. Needle Safety Activation Force
128 performance after preconditioning over the proposed shelf-life to the appropriate
129 reliability (95%/99%) remains unresolved and should be provided to ensure reliable
130 deployment of the safety feature.

131

132

133

Question 4:

Does the FDA agree that the use of (b) (4) month real-time aged devices in combination with the additional supportive information proposed, is acceptable to claim 36 months shelf-life?

FDA Response to Question 4:

No, we do not agree with your proposal to use (b) (4) months real-time aged devices in combination with your supportive information to claim 36 months. As discussed in the prior teleconference and CRL deficiency, needle safety performance is dependent on the drug product in the syringe and combination product manufacturing (assembly and packaging). Therefore, reference to 4 years of performance data generated by (b) (4) is not considered supportive data. We (b) (4) nth shelf-life based on (b) (4) months. You may extend your shelf-life to 36 months via an annual report.

Question 5:

Does the FDA agree that by addressing the testing elements above satisfactorily, this will constitute a complete response and approval for tralokinumab?

FDA Response to Question 5:

See FDA Responses to Questions 1-4.

Question 6:

The FDA conducted a Pre-License Inspection (PLI) of the AstraZeneca's Frederick Manufacturing Center on March 2-19, 2021. A Form FDA 483 was issued on March 19, 2021, and AstraZeneca's responses to Form FDA 483 were submitted on April 8, 2021. As the CRL did not contain any items related to facility product quality observations, LEO Pharma understands that the Form FDA 483 response provided by the facility met the FDA's expectations. Therefore, the Sponsor seeks to confirm the following:

- a. Does the FDA affirm our understanding that the absence of any facility product quality observations in the CRL is an indicator that there are no substantive issues pertaining to the PLI that will impact approval of the BLA?
- b. Does the FDA require submission of additional information to finalize the evaluation of the PLI?
- c. Does the FDA anticipate the need for a re-inspection after BLA resubmission?

FDA Response to Question 6:

We confirm that no substantive issues pertaining to the drug substance (DS) facility PLI that will impact approval of the BLA. We do not require submission of additional information to finalize the evaluation of the PLI. We do not anticipate the need for a re-inspection of the DS facility after BLA resubmission.

2.2. Clinical**Question 7:**

In reference to the requested safety update, does the FDA agree to the following:

- a. To use the format of the already submitted 120-Day Safety Update for the requested tralokinumab safety update?
- b. To present the safety data from the newly completed ECZTRA 4 (drug-drug interaction) and ECZTRA 7 (non-IND Phase 3) trials separately for comparison with that of the monotherapy and AD pool?
- c. To use the proposed cut-off date, March 31, 2021 (or maximum 6 months prior to re-submission), for the ongoing clinical trials?

FDA Response to Question 7:

Your proposed format for the safety update and presentation of safety data from trials ECZTRA 4 and ECZTRA 7 appears acceptable.

Question 8:

In reference to the following PMR description, (b) (4)

(b) (4) does the FDA agree that the Amended Agreed Initial Pediatric Study Plan (iPSP) dated 28 February 2020 could fulfill this PMR?

FDA Response to Question 8:

Your overall stepwise pharmacokinetic (PK) assessment plan appears reasonable; however, you could consider a lead-in PK assessment plan in a sub-set of subjects 6 months to less than 2 years of age to provide additional support for dosing. The subjects that participate in the lead-in PK assessment should continue in the trial. Adequacy of data to fulfil the PMR for stepwise PK assessment will be a review issue

Question 9:

In reference to the following PMR descriptions:

- “A prospective, registry-based, observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to tralokinumab during pregnancy to an unexposed control population”
- “A retrospective cohort study using electronic medical record data” (Note. – Outline of the protocol reviewed by the FDA)

LEO Pharma plans to include the below timetables in the BLA resubmission to fulfill the pregnancy outcomes studies PMRs. In addition, LEO Pharma plans to submit the protocols for these studies to the IND, subsequent to BLA approval and understands that there are no FDA’s expectations to include draft protocols in the BLA resubmission. Does the FDA agree with this approach?

221 **FDA Response to Question 9:**

222 The timeline awaits input from the Pediatric Review Committee.



244 **2.3. Regulatory**

245
246 **Question 11:**

247 Pursuant to MAPP 6020.4, does the FDA preliminarily agree that LEO Pharma's
248 complete response to the CRL may be classified as a Class 1 resubmission with a 2-
249 month review clock?

250
251 **FDA Response to Question 11:**

252 No. We do not agree. Your resubmission to address the deficiencies in the
253 April 23, 2021 Complete Response would not be classified as minor clarifying
254 information per the MAPP 6020.4 *Classifying Resubmissions of Original NDAs,*
255 *BLAs, and Efficacy Supplements in Response to Complete Response Letters* and
256 therefore would be a Class 2 resubmission.

257
258 **Question 12:**

259 Provided a Class 1 resubmission is granted, can the FDA accommodate a
260 proprietary name request review within the 2-month Class 1 resubmission timeline?

261
262 **FDA Response to Question 12:**

263 See FDA Response to Question 11.

264
265

266 **Question 13:**
 267 LEO Pharma proposes that a resubmission containing the module components
 268 outlined in Table 4 would constitute a complete response (assuming such
 269 components address the deficiencies noted in the CRL) and that they are sufficient
 270 to support the approval of BLA 761180. Does the FDA concur?

271
 272

Table 4

Module 1	Module 2	Module 3
1.1.2 Form FDA 356h	3.2.R.3.4 Device Design Verification	5.3.5.3 ISS (<i>modeled to 120-day safety update</i>)
1.2.1 Cover letter	3.3 Literature References	<ul style="list-style-type: none"> • Case report forms and narrative summaries for each patient who died or did not complete a trial because of an adverse event. • Narrative summaries for serious adverse events.
1.6.1 Meeting request – Type A meeting request		
1.6.2 Meeting background materials – Type A meeting package		
1.6.3 Correspondence regarding meetings <ul style="list-style-type: none"> • Mid-cycle communication and minutes • Late-cycle meeting package and minutes • DL review letter 		
1.6.3 Correspondence regarding meetings		
1.9.4 Proposed pediatric study request and amendments		
1.11.1 Quality information amendment		
1.11.4 Multiple module information amendment		
1.14.1.2 Annotated draft labeling text		
1.14.1.3 Draft labeling text		
1.14.5 Foreign labeling		
1.18 Proprietary names		

273
 274
 275
 276
 277

FDA Response to Question 13:

The proposed outline appears appropriate for review.

278 **3.0 ADMINISTRATIVE COMMENTS**279
280 **NONPROPRIETARY NAME**

281
282 On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming*
283 *of Biological Products*, stating that, for certain biological products, the Agency intends to
284 designate a proper name that includes a four-letter distinguishing suffix that is devoid of
285 meaning.

286
287 Please note that certain provisions of this guidance describe a collection of information
288 and are under review by the Office of Management and Budget under the Paperwork
289 Reduction Act of 1995 (PRA). These provisions of the guidance describe the
290 submission of proposed suffixes to the FDA, and a sponsor's related analysis of
291 proposed suffixes, which are considered a "collection of information" under the PRA.
292 FDA is not currently implementing provisions of the guidance that describe this
293 collection of information.

294
295 However, provisions of the final guidance that do not describe the collection of
296 information should be considered final and represent FDA's current thinking on the
297 nonproprietary naming of biological products. These include, generally, the description
298 of the naming convention (including its format for originator, related, and biosimilar
299 biological products) and the considerations that support the convention.

300
301 To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA
302 will assign a four-letter suffix for inclusion in the proper name designated in the license
303 at such time as FDA approves the BLA.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STROTHER D DIXON
06/08/2021 11:41:40 AM



IND 123797

MEETING MINUTES

LEO Pharma A/S
c/o LEO Pharma Inc.
Attention: Zhengyu Liu, PhD
Director, US Regulatory Affairs
7 Giralda Farms, 2nd Floor
Madison, NJ 07490

Dear Dr. Liu:¹

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

We also refer to the meeting between representatives of your firm and the FDA on May 1, 2019. The purpose of the meeting was to discuss the development program for tralokinumab injection.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Strother D. Dixon, Senior Regulatory Project Manager at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Sponsor Response to Preliminary Comments

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: May 1, 2019; 9:00 – 10:00 AM ET
Meeting Location: FDA, White Oak Building 22

Application Number: IND 123797
Product Name: tralokinumab injection
Indication: For the treatment of atopic dermatitis (AD)
Sponsor Name: LEO Pharma A/S

Meeting Chair: Kendall A. Marcus, MD
Meeting Recorder: Strother D. Dixon

FDA ATTENDEES

Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Shari Targum, MD, MPH, Associate Director for Biosimilars, DDDP
David Kettl, MD, FAAP, Clinical Team Leader, DDDP
Roselyn E. Epps, MD, Clinical Reviewer, DDDP
Mohamed Alosh, PhD, Biometrics Team Leader, Division of Biometrics (DB) III
Marilena Flouri, PhD, Biometrics Reviewer, DB III
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Clinical Pharmacology (DCP) III
Cindy Pan, PhD, Senior Staff Fellow, DCP III
Jessica Hankins, PhD, Microbiologist, Division of Microbiology Assessment, Branch IV
Candace Gomez-Broughton, PhD, Microbiologist, Division of Microbiology Assessment, Branch IV
Pengfei Guo, PhD, Quality Reviewer, Division of Biotechnology Review and Research (DBRR) II
William Hallett, PhD, Biologist, DBRR II
Jacqueline Gertz, PhD, Biomedical Engineer, Center for Devices Radiological Health /Office Health Technology 3/Division of Health Technology 3C
Sevan H. Kolejian, PharmD, MBA, Team Leader, Division of Medication Error Prevention and Analysis (DMEPA)
Madhuri R. Patel, PharmD, DMEPA Safety Evaluator
Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Anders Rosholm, MSc, PhD, Project Statistician
Thomas Nedergaard Jensen, Cand, Pharm, Project Vice President
Jette Vestergaard Olsen, Cand. Pharm, Senior Global Regulatory Lead

Mads Gjelstrup Kristensen, MSc Eng, Principal Regulatory Specialist
Per Soerensen, MSc Stat, Biostatistics Lead
Jens Stampe Soerensen, Principal Statistical Programmer
Bo Bang, Medical Director, MD, PhD, Medical Director
Christina Kerre Olsen, MSc (Cand Pharm), PhD, Senior Medical Science Leader
Katja Wendicke Lophaven, MSc (Pharm), Senior Global Medical Science Lead
Joergen Schutzsack, DVM, DABT, ERT, Associate Director Toxicology
Lars Lindgaard Hansne, PhD (Pharma) Senior Manager
Lene Tegllund Thomsen, MSc Pharm, Principal Scientist, CMC
Kristine Noergaard Strandfelt, MSc, PhD, Senior Safety Advisor
Anders Soehoe., MSc, Pharm, PhD, Clinical Pharmacologist
Zhengyu Liu, PhD, Director, US Regulatory Affairs
Dorreen Morgan, PharmD, MS, Vice President, US Regulatory Affairs and QA

1.0 BACKGROUND

Purpose: To discuss the development plan for tralokinumab injection for the treatment of atopic dermatitis.

Regulatory Correspondence History

We have had the following meetings/teleconferences with you:

- November 19, 2018 – Type C/Guidance Written Responses Only
- February 14, 2017 – Type C/Guidance Written Responses Only
- January 30, 2017 – Type C/Guidance Written Responses Only
- September 7, 2016 – Type B/End-of-Phase 2

We have sent the following correspondences:

- March 29, 2019 – Advice
- February 27, 2019 – Information Request
- October 24, 2018 – Advice
- October 16, 2018 – Advice
- September 21, 2018 – Advice
- July 20, 2018 – Advice/Information Request
- June 28, 2018 – Pediatric Study Plan Initial Agreement
- March 23, 2018 – Advice
- February 9, 2018 – Advice
- December 20, 2017 – Advice
- December 15, 2017 – Information Request
- November 17, 2017 – Advice
- August 22, 2017 – Advice

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

- June 23, 2017 – Advice
- June 6, 2017 – Pediatric Study Plan Initial No Agreement
- May 22, 2017 – Advice
- February 3, 2017 – Pediatric Study Plan Written Response
- December 11, 2014 – Study May Proceed

FDA sent Preliminary Comments to LEO Pharma A/S on April 26, 2019.

2. DISCUSSION

2.1. Regulatory

Question 1:

Does the Agency agree with the proposed dossier content (TOC) for Modules 1, 2, 3, 4, and 5 of the tralokinumab BLA?

FDA Response to Question 1:

From a technical standpoint (not content related) yes, the proposed format for the planned BLA is acceptable except for below sections:

- According to CTOC, “Container closure system” must be placed in section 3.2.P.7 and “Description of Manufacturing Process and Process Controls” must be placed in section 3.2.P.3.3. For all of the sections highlighted in below screenshot, refer to The Comprehensive Table of Contents Headings and Hierarchy located at <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163175.pdf>

Module	Comments
3.2.P.2 Pharmaceutical development	
3.2.P.2.1 Components of Drug Product	<ul style="list-style-type: none"> • Drug Substance and Excipients.
3.2.P.2.2 Drug Product	<ul style="list-style-type: none"> • Drug Product. • Formulation Development. • Overages. • Physicochemical and Biological Properties.
3.2.P.2.3 Manufacturing Process Development	<ul style="list-style-type: none"> • Quality Risk Management. • Critical Quality Attributes. • Manufacturing Process History. • Comparability during Process Development. • Process Characterization: Overview, Process Steps, Environmental Impacts, Critical Process Parameters, Leachables Risk Assessment.
3.2.P.2.4 Container Closure System	
3.2.P.2.5 Microbial Attributes	
3.2.P.2.6 Compatibility	

- According to eCTD guidelines, “CRFs and Individual Patient Listings” must be submitted under 5.3.1 through 5.3.5 (Please see guidelines) and not 5.3.7.

Question 2A:

Does the Agency concur that the ECZTRA 1, 2, and 3 constitute “covered clinical studies” for the purpose of complying with financial disclosure requirements?

FDA Response to Question 2A:

Yes, we agree.

Question 2B:

Does the Agency agree with Sponsor’s proposal for provision of summary level clinical site data for the covered clinical trials?

FDA Response to Question 2B:

To allow for timely review of your BLA after submission, your clinical site data for the covered clinical trials should be submitted in the proper format and level of detail. Refer to guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*.

2.2 Chemistry, Manufacturing, and Controls (CMC)

Question 3:

Does the Agency intend to undertake a Prior Approval Inspection at the Drug Substance and Drug Product manufacturing sites and if so, does the Agency require to see the product of interest in active manufacturing?

FDA Response to Question 3:

The Agency's determination of an establishment inspection for the drug substance and drug product manufacturing sites will be made once biologics license application (BLA) is received. The drug substance facility should be manufacturing the product under review during the inspection. If the tralokinumab drug product (DP) is not being manufactured at the time of inspection, the Agency may consider conducting the DP inspection during the manufacture of a representative process similar to the tralokinumab process (e.g., product fill or media fill). Refer to the CMC microbiology comments for additional information.

Question 4A:

Does the Agency agree with the proposal to cross-reference the stated facility DMFs for the Drug Substance and Drug Product manufacturing sites in lieu of providing this information in Section 3.2.A.1 of the tralokinumab BLA submission?

FDA Response to Question 4A:

Yes, we agree with your proposal to cross-reference the Type V facility DMFs, DMF (b) (4) DMF 024888 for Catalent Indiana in lieu of providing the information in Section 3.2.A.1. Note that a description of the drug substance manufacturing process and the supporting validation data should be submitted to the BLA. Additionally, validation information and data in support of the drug product sterility assurance should be included in the BLA rather than cross-referenced to a DMF. Information on media fills, environmental monitoring, sterilization and depyrogenation of equipment and components in direct contact with the sterile product should be contained within Section 3.2.P.3.5 Process Validation and/or Evaluation of the BLA. Refer to the CMC microbiology comments for additional information.

Question 4B:

Does the Agency agree with the proposal to cross-reference the stated Container Closure system DMFs for Drug Product?

FDA Response to Question 4B:

Yes, we agree with the proposal to cross-reference the stated Container Closure DMFs, DMF (b) (4) and DMF (b) (4). Refer to the CMC microbiology comments for additional information.

Note that the applications need to include the appropriate prefix in the href links (e.g. xlink:href=".../indXXXXXX/0009/m2/24-nonclin-over/nonclinical-overview.pdf"). In the leaf titles of the documents, it is recommended that the leaf title indicate the words "cross reference to" and the application number (e.g. Cross Ref to indXXXXXX). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application.

Question 5:

Does the Agency agree that Drug Product stability data at the 36-month timepoint under long term conditions for three manufacturing scale lots (031C17, 032C17, 033C17), providing data at the proposed three year shelf life, can be provided four months after the BLA submission date without being considered a substantial amendment subject to extension of the BLA goal date?

These 36-month data will supplement the data up to (b) (4) months provided for these lots in the initial BLA submission.

FDA Response to Question 5:

Yes, we agree with the proposed stability update to provide the 36-month timepoint for the three drug product lots four months after BLA submission without extending the goal date.

1. In order to support your proposed dating period for drug product, you may wish to provide a "simple stability update" which is defined as follows: Stability data and analyses performed under the same conditions and for the same drug product batches in the same container closure system(s) as described in the stability protocol provided in the original submission.
2. This update will use the same tabular presentation as in the original submission as well as the same mathematical or statistical analysis methods (if any) and will not contain any matrix or bracketing approaches which deviate from the stability protocol in the original BLA/NDA. Simple stability updates submitted up to month 7 for a standard submission and month 4 for a priority submission will be reviewed and considered in shelf life determinations.

Question 6:

Does the Agency agree on the submission strategy for the accessorized prefilled syringe functional performance information and human factors studies to be included in 3.2.R?

FDA Response to Question 6:

The information provided is very high level, therefore only high level comments can be provided. The following information should be provided in module 3.2.P:

- The following feedback is related to the device constituent parts of your combination product. As the owner of the combination product it is expected that you maintain the quality control strategy, including design controls, for the device constituent parts of your product.
- For more information regarding cGMP requirements for combination products please refer to the FDA guidance titled guidance for industry and FDA Staff: *Current Good Manufacturing Practice Requirements for Combination Products* issued in January 2017 (<https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf>).
- You should identify the subset of design requirements necessary for your device constituent to safely and effectively achieve the combination product's intended use. For reference, this subset of design requirements should be referred to as Essential Performance Requirements (EPRs). Other internally established terminology, such as Critical Quality Attributes (CQAs), Key Performance Indicators (KPIs), etc. may be considered equivalent to EPRs if the definition is consistent with that of EPRs and the requirements are applied to the control strategy in the same manner as EPRs. Your EPRs should consider the desired level of reliability of the product and level of risk associated with failure.
- If you intend to refer to documentation (e.g. verification test reports) held within another submission and/or master file, be sure to provide a letter of authorization or right of reference alongside a detailed description of the location of the information within the file (i.e. volume, page number, section header, etc.). It is recommended that you provide a brief overview of how the referenced information is intended to support the review of your submission.
- It is recommended that you refer to the *eCTD Technical Conformance Guide* published in September 2016 (<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf>) when determining the location of the following information within your submission.

Provide the following information, at a minimum, to support the device constituent parts of the combination product:

- 1) Device Description Documentation
 - a) A complete and detailed description of your device constituent design and delivery system, including any novel features and/or functionalities. This may include engineering drawings and detailed descriptions of the individual device constituent components.
 - b) The principles of operation of your device, from beginning to end of the activation process, in which you explain the drug delivery mechanisms (e.g. mechanical, electrical, etc.) of your device constituent.

- c) If the device constituent is being used in an investigational manner, include device labeling stating that the device is for investigational use only.

2) Design Control Documentation

- a) Design Inputs/Outputs – A complete and detailed description of the device constituent design inputs and outputs per 21 CFR 820.30, specifically the design requirements/specifications documentation with objective acceptance criteria. Ensure that you clearly describe the acceptability of your design inputs and outputs within the context of the intended use of your combination product. The design inputs and outputs should be developed in accordance with the risk profile of the entire combination product and may vary depending on the indications for use, patient and/or user population, environment of use, etc.

(i) EPR Identification –

For pre-filled syringes, we recommend that the EPRs include, at a minimum, the following:

- Dose Accuracy
- Break loose / Glide Force

- b) Design Verification Documentation – Verification testing documentation should include summary test results of established test methods for the product (e.g. recognized consensus standards, FDA Guidance, etc.) or complete verification test reports for unique or unrecognized test methods. All verification testing should be directly traced to the design inputs of the device constituent. Ensure that you utilize test methods and preconditioning that simulate the intended use of your product. You should use a statistically significant sample size for verification testing. Provide valid justifications for the acceptability of any test results that do not pass its acceptance criteria.

- (i) As part of design verification, you should verify the EPRs with the to-be-marketed version of the device constituent and the intended biologic/drug product. However, if you plan to rely on verification testing conducted with a surrogate be sure to provide a scientific rationale for the acceptability of the surrogate for the intended biologic/drug product (i.e. fluid characteristics, viscosity, etc.). If available, results of stability/shelf-life testing may be provided if the to-be-marketed version of the device constituent and intended drug/biologic product are used.

- c) Risk Analysis Documentation – Provide a risk analysis associated with the final finished combination product that is inclusive of risks associated with the device constituent parts of the combination product. Your risk analysis should include all identified risks, potential hazards that are apparent to your device, risk control measures and/or mitigation strategies, verification of risk control and/or mitigation measures, and the clinical acceptability of any residual risk

associated with the device. You should outline the methods in which you identified the risks of the product within your risk analysis documentation (e.g. DFMEA, UFMEA, Fault Tree Analysis, etc.). Refer to recognized consensus standard ISO 14971 “Medical devices - Application of risk management to medical devices” or device specific Guidance for more details.

- d) Design Validation Documentation – Provide design validation information demonstrating that devices conform to defined user needs and intended uses. Design validation information should be from production units (or equivalents) under actual or simulated use conditions.
- e) Stability / shelf-life testing and shipping studies. You should provide documentation that ensures the to-be-marketed version of the combination product maintains the EPRs up to the labeled date of expiry and after actual and/or simulated shipping.

If you plan to use a test subject other than the to-be-marketed version, you should list the differences in the design and provide a risk-based assessment demonstrating how the differences do not significantly impact the product’s EPRs. Stability/shelf-life testing and shipping studies may be incorporated into design verification testing.

- f) Lot release specifications. In your lot release specifications include the EPRs. If you intend to propose alternative control strategies for the EPRs, we recommend requesting specific feedback regarding your strategy.

3) Traceability Documentation

It is recommended that a traceability matrix is provided to ensure 1) the design outputs are adequately verified to meet the design inputs and 2) the finished combination product is validated to meet the user needs. It is highly recommended that the EPRs are highlighted for ease of review. While a traceability matrix can take many forms, the Agency has provided a high-level example for reference:

Patient / User Needs	Design Input(s)	Design Output(s)	Verification	Validation	Shelf Life / Stability (Y/N)*	Shipping (Y/N)*	Lot Release (Y/N)*

*These columns are applicable only for EPRs

- 4) Considerations specific to your device constituent
 - a) Biocompatibility evaluation – You should provide documentation to support the biocompatibility of your device constituent including test reports and protocols to ensure that the system components are biocompatible commensurate with the level and duration of patient contact. Refer to the FDA Guidance titled Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" – Guidance for Industry and Food and Drug Administration Staff issued in June 2016 (<https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf>) for more details.

We recommend that you submit Human Factors (HF) data to support your BLA application under eCTD Section 5.3.5.4 – Other Study reports and related information.

We acknowledge that you submitted an HF validation protocol on March 1, 2019. You should expect an advice letter issued on April 24, 2019 that contains our recommendations for your Human Factors validation study protocol.

Meeting Discussion:

The sponsor proposed placing the Human Factors (HF) studies reports in module 3.2.R of the eCTD. The Agency recommended placing a reference document in section 5.3.5.4 linking to HF data submitted in module 3.2.R and referencing the information in the cover letter.

Additional CMC Microbiology Comments:

The FDA is providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 351(a) BLA submission.

All facilities should be registered with the FDA at the time of the 351(a) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the drug substance and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.

Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

The CMC Drug Substance section of the 351(a) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The information should include, but not be limited to the following:

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

- Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).
- Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
- Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).
- Information and summary results from the shipping validation studies (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications (3.2.S.4).
- Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).

The CMC Drug Product section of the 351(a) BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA guidance for industry *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf>.

- The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.
- Identification of the manufacturing areas and type of fill line (e.g. open, RABS, isolator), including area classifications.
- Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use

integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.

- Parameters for filling and plunger placement for the pre-filled syringes.
- A list of all equipment and components that contact the sterile drug product (i.e. the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.
- Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.
- Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5, as appropriate:

- Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.
- Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.
- In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.
- Isolator decontamination summary data and information, if applicable.
- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.
- Information and summary results from shipping validation studies. For prefilled syringes, the effects of varying air pressure on pre-filled syringe plunger movement and potential breaches to the integrity of the sterile boundary during shipment should be addressed. Include data demonstrating that the pre-filled

syringe plunger movement during air transportation does not impact product sterility.

The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

- Container closure integrity testing. System integrity should be demonstrated initially and during stability. Data demonstrating the maintenance of container closure integrity after the assembly of the pre-filled syringe and autoinjector should be included. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed *in lieu* of sterility testing for stability samples every 12 months (annually) until expiry.
- Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers. Provide full descriptions and validation of non-compendial rapid microbial methods.
- Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).

Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> *Bacterial Endotoxin Test* (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time.

2.3 Nonclinical

Question 7:

Does the Agency agree that the nonclinical development program and the outlined content of the nonclinical part of the application are adequate to support a substantial review of the application for the proposed indication?

FDA Response to Question 7:

We agree that your nonclinical development program and the outlined content of the nonclinical part of the application appear acceptable to support your BLA submission. However, include a Toxicology Tabulated Summary in Module 2.

You stated that a comprehensive assessment of the carcinogenic potential of your product was performed that integrated data from repeat-dose toxicity studies with

evaluation of generalized immune suppression, and evaluation of published literature through end June 2018. Provide an updated carcinogenicity risk assessment for your product with your BLA submission.

2.4 Clinical/Biostatistics/Clinical Pharmacology

Question 8A:

Does the Agency agree that the tralokinumab AD program, including the pivotal phase 3 trials ECZTRA 1, 2, and 3 and the supportive clinical trials ECZTRA 5 and D2213C00001, combined with PK and safety data from tralokinumab used in other indications, will provide the complete documentation required to file and to support a substantial review of the application for the proposed indication?

FDA Response to Question 8A:

The elements you propose above appear adequate for filing. To receive approval to market a product for a specific indication, an applicant must present substantial evidence of the safety and efficacy of their product for that indication.

Question 8B:

Does the Agency accept that the results from the phase 1 DDI trial (ECZTRA 4) will be submitted as a post-approval commitment?

FDA Response to Question 8B:

We acknowledge that your clinical DDI study (ECZTRA 4) is ongoing and may not be completed timely due to the difficulties of recruitment, and you propose to submit the results from the DDI study as a postmarketing commitment. Your proposal appears acceptable.

Question 9A:

Does the Agency agree to LEO's proposal to unblind ECZTRA 1, 2, 3, and 5 when all randomized subjects have finished the blinded treatment periods and that the complete safety follow-up data for all subjects from ECZTRA 1, 3, and 5 will be available for review at submission of the 120-day safety update?

FDA Response to Question 9A:

We agree with your proposal. Please be aware that safety concerns may result in the need for an Advisory Committee (AC) meeting.

Question 9B:

Does the Agency agree to LEO's proposal to report CTRs for ECZTRA 1 and 2 based on DBL 2 data at the time of the BLA submission?

FDA Response to Question 9B:

Your proposal appears reasonable.

Question 9C:

Does the Agency agree to LEO's proposal to report CTRs for ECZTRA 3 and 5 based on DBL 1 data (including all available safety follow-up data) at the time of the BLA submission?

FDA Response to Question 9C:

We do not agree. Analysis of safety data at the end of DBL 2 will include all US and European subjects. At the end of DBL 1, 339 subjects will have incomplete safety data, the majority of which will be enrolled in the monotherapy study.

Meeting Discussion:

The sponsor clarified the safety data that would be submitted at the time of BLA submission will include 930 subjects who will have completed 52 weeks. Data on additional 115 subjects in off treatment safety follow-up will be submitted in the 120-day safety update report. The Agency responded that this would be reasonable. If an Advisory Committee (AC) is held, we would need sufficient time to review such data prior to the AC.

Question 10A:

Does the Agency agree with the proposal for the placement of the planned integrated analyses of efficacy and safety data from trials in AD within the BLA?

Question 10B:

Does the Agency concur with the proposal for the placement of the planned integrated analyses of safety data from trials in other indications in the BLA?

FDA Responses to Question 10A and 10B:

FDA agrees to the eCTD location of ISS and ISE.

Question 11:

Does the Agency concur with LEO's proposal for data format, documentation, and the plan for data conversion for the clinical trials in AD as well as the clinical trials from other indications?

FDA Response to Question 11:

Your proposal to submit datasets according to CDISC formatting is acceptable.

You plan to use the Multiple Imputation (MI) approach for the handling of missing data in ECZTRA 3. The MI approach involves generating multiple datasets, and therefore, instead of submitting the multiple imputed datasets, submit the SAS code used to implement MI. In addition, submit the SAS code used to analyze these datasets.

For the analysis datasets, we have the following comments:

- Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.
- The analysis dataset documentation (Define.xml) should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables. For ease of viewing by the reviewer and printing, submit corresponding Define.pdf files in addition to the Define.xml files.
- In addition to the electronic datasets, you should submit study protocols and statistical analysis plans, all protocol amendments (with dates), generated treatment assignment lists, and the actual treatment allocations (along with the date of enrollment).

Question 12:

Does the Agency agree with the proposed approach for evaluation of QTc prolongation?

FDA Response to Question 12:

Tralokinumab is a human monoclonal antibody of IgG4. To date, there is no evidence of drug-induced QTc prolongation observed in the Phase 1 trials in healthy subjects and subjects with asthma and Phase 2 dose-finding trial in subjects with AD (D2213C00001). We acknowledge that you are routinely monitoring ECG in all ongoing trials for subjects with AD and you plan to report the ECG results in the individual CTRs in Module 5 and in the safety evaluation in Module 2.7.4 during your submission. *Your proposed approach for evaluation of QTc prolongation appears acceptable.*

Question 13:

Does the Agency agree with the approach for the BLA regarding external references such as literature and guidelines?

FDA Response to Question 13:

You stated that you intend to use external references as needed in the BLA in the nonclinical and clinical overviews (Module 2.4 and 2.5), the clinical summaries (Module 2), and in the individual clinical trial reports (located in Module 5). Whether or not your external references provide sufficient evidence to support approval and marketing of your product remains a review issue.

Question 14:

Does the Agency agree on the content and the trials planned to be included in the summary of clinical pharmacology (M2.7.2)?

FDA Response to Question 14:

We acknowledge that you plan to summarize pharmacokinetic (PK) results from 4 of 6 completed Phase 1 trials in the Summary of Clinical Pharmacology Studies (Module 2.7.2). Because 2 Phase 1 trials are not considered relevant for the proposed AD BLA submission. Your proposal appears reasonable.

In addition to the Phase 1 PK trials, you should briefly summarize results of individual Phase 2 and 3 studies which support the selection of dose, dosage schedule, and formulation of the final product in the Module 2.7.2 as well. Generally, the Summary of Clinical Pharmacology Studies (Module 2.7.2) should include 1) background and overview, 2) summary of results of individual studies, 3) comparison and analyses of results across studies, 4) Special studies, and 5) Appendix. Refer to M4E(R2): *The CTD-Efficacy Guidance for Industry* for more information.

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM465221.pdf>

Question 15A:

Based on the description provided in the population PK analysis plan, does the Agency agree to the suggested approach for the structural model?

FDA Response to Question 15A:

Your suggested approach for the structural model appears acceptable.

Question 15B:

Based on the information provided in the population PK analysis plan, does the Agency agree to the suggested approach for the covariate analysis?

FDA Response to Question 15B:

Your proposed approach appears reasonable.

Question 16A:

Does the Agency consider the modified plan for multiplicity adjustment to control Type I error rate acceptable for ECZTRA 1, 2, and 3?

FDA Response to Question 16A:

We reiterate our previously conveyed comment (see 'Written Responses' dated February 14, 2017) that formal statistical testing against subjects re-randomized to placebo for maintenance is not meaningful, and therefore, maintenance endpoints should not be included in the multiplicity adjustment plan. Again, we note that descriptive analyses/statistics for maintenance, such as proportion of subjects who

maintain their response over the maintenance of period and time to relapse after treatment withdrawal can be presented in the label.

In addition, we reiterate our comment (see advice letter dated September 21, 2018) that change in SCORAD and change in DLQI from baseline to Week 16 may not translate into clinically meaningful treatment effects, and therefore, may not be included in the label. See also our response to Question 17.

Meeting Discussion:

The sponsor acknowledged the Agency's comments that formal testing during the maintenance period and testing for DLQI and SCORAD endpoints are not required as finding from this testing is not going to appear in labeling. The sponsor clarified that including such endpoints in their testing strategy is intended for scientific publication.

In addition, the Agency confirmed that significant results for the secondary endpoint based on pruritus may appear in labeling.

Question 16B:

Does the Agency agree with the Sponsor's proposal to introduce the modifications to the testing hierarchies via the statistical analysis plan, which will be finalized before unblinding of the trials?

FDA Response to Question 16B:

You plan to introduce the modifications to the testing hierarchies via the statistical analysis plan, which will be finalized before unblinding of the trials. You should submit the statistical analysis plans for all pivotal Phase 3 trials well before unblinding the trials for Agency review and comments to ensure the integrity of the trials. Full details regarding the analysis methods and the methods for handling the missing data for the primary and secondary endpoints should be included in the statistical analysis plans for all Phase 3 trials.

Meeting Discussion:

The sponsor noted that modifications in the statistical analysis plan (SAP) have already been described in the briefing package for the Pre-BLA meeting. The sponsor clarified that they will submit the modified SAP to the Agency before unblinding the data. The Agency agreed that the sponsor can proceed of the unblinding of the data without the Agency's review of the submitted SAP.

Question 17:

Does the Agency agree that the proposed primary and sensitivity analyses for the different estimands meet the Agency's expectations for evaluating efficacy in terms of SCORAD and DLQI?

FDA Response to Question 17:

The DLQI does not appear to be fit-for-purpose in the context of this drug development program due to lack of item relevancy. The DLQI contains questions that measure broad concepts related to general skin conditions (e.g., going shopping, making your home messy) which may lack clinical relevance and be insensitive to treatment effect among atopic dermatitis patients. Further, there are issues surrounding content validity, specifically the use of multi-barreled questions (questions measuring more than one concept) which can be problematic from a measurement standpoint. The Agency addressed SCORAD use in a previous advice letter.

Question 18A:

Does the Agency agree with the proposed pooling strategy for the integrated analyses of efficacy?

FDA Response to Question 18A:

Your proposed pooling strategy is acceptable; however, it should be noted that the objective of the integrated summary of efficacy (ISE) is to support the analysis results obtained from the individual trials and not to establish a new efficacy claim based on pooling data from the individual trials. Therefore, analyses based on pooled efficacy data are considered exploratory. Establishing an efficacy claim would be based on efficacy data from the individual Phase 3 trials along with a replication of study findings.

Question 18B:

Does the Agency agree with the proposed subgroups to be analyzed for the primary endpoints (IGA 0/1 and EASI75)?

FDA Response to Question 18B:

You propose to conduct subgroup analysis for the primary endpoints using the monotherapy pool. See our response to Question 18A regarding analyses based on pooled data.

Question 19A:

Does the Agency agree that the total accrued exposure in the AD trials is adequate to support the safety review of the BLA for the proposed indication?

FDA Response to Question 19A:

The total accrued exposure appears adequate for filing.

Question 19B:

Does the Agency agree with the proposed pooling strategy for safety including integrated safety data from trials in AD (AD pool and monotherapy pool)?

FDA Response to Question 19B:

The proposed pooling strategy for AD and monotherapy appears reasonable, as long as the studies are for the proposed indication. In your ISS you may present safety results for the proposed AD pooled data in addition to the monotherapy pool.

The proposed pooling strategy in the monotherapy pool for safety (i.e., simple pooling) appears reasonable since the randomization ratios in ECZTRA 1 and 2 are the same. The proposed pooling strategy in the AD pool for safety (i.e., CMH weighting principle) appears reasonable since the randomization ratios in the pooled trials differ. However, while the AD pool includes data from 5 trials (ECZTRA 1, 2, 3, 5 and D2213C00001), in Section 11.3.4.3 of your briefing package you describe that the CMH weighting principle will be applied for pooling data from 3 trials. Clarify whether the CMH weighting principle will be applied to pool data only from 3 trials and specify which trials will be pooled, or whether the CMH weighting principle will be applied to all 5 trials included in the AD pool.

Question 19C:

Does the Agency concur with LEO's proposal for including integrated safety information from clinical trials in asthma (asthma pool)?

FDA Response to Question 19C:

We agree with your proposal to include integrated safety information from your asthma trials.

Question 19D:

Is the approach regarding the exposure pool (including all trials in all indications) adequate for the evaluation of exposure, deaths, pregnancies and rare events?

FDA Response to Question 19D:

You define the exposure pool as data from all phase 1 to 3 trials with tralokinumab, including AD, healthy subjects, asthma, UC and IPF. In addition to providing a summary of deaths, pregnancies, and rare events, we recommend that you provide a summary of MACE events using the exposure pool (as well as the AD pool).

Question 19E:

Does the Agency agree with the proposed subgroups (Table 8) to be analyzed for safety (monotherapy pool only)?

FDA Response to Question 19E:

Yes, we agree.

Question 20:

Does the Agency agree with the proposal for safety areas of interest to be included in the BLA, including the pre-defined AESIs as well as other safety areas of interest based on pre-defined MedDRA search criteria?

FDA Response to Question 20:

We recommend that you select adverse events of special interest (AESI) based on the mechanism of action of drug, animal toxicity data, and possible class effects. Include serious infections, opportunistic infections, malignancies, tuberculosis, major adverse cardiac events (MACE). Consider adjudication by independent, blinded, subspecialty adjudicators, if appropriate.

Question 21A:

Does the Agency agree to this proposal for data included in the 120-day safety update report?

FDA Response to Question 21A:

We agree with your proposal. See response to Question 9A.

Question 21B:

Does the Agency agree with the proposal for the data cut-offs to be included in the BLA?

FDA Response to Question 21B:

Your cut-off dates should ensure that your safety database is adequate for filing, and that your safety data are complete and sufficient to allow for timely review.

Question 22:

Does the Agency agree with LEO's proposal for submission of narratives and CRFs in the BLA and the 120-day safety update?

FDA Response to Question 22:

We agree with your proposal.

Question 23A:

Does the Agency agree to the planned integrated analysis for investigating immunogenicity in the AD pool?

Question 23B:

Does the Agency concur that for all other trials than the ECZTRA trials in the AD pool, the immunogenicity evaluation will be based on results from the individual CTRs?

FDA Response to Question 23A and 23B:

Two ADA assays have been developed and validated during your AD drug development. The original ADA assay developed by AstraZeneca was used in the Phase 2b dose-finding trial (D2213C00001), and the updated ADA assay developed by the Sponsor is currently used for ECZTRA trials. We note that the updated ADA assay has a higher tralokinumab tolerance than the original ADA assay.

You propose to use a sub-dataset (ADA ECZTRA analysis set) to evaluate the impact of immunogenicity on the PK, safety, and efficacy of tralokinumab with or without topical corticosteroids (TCS) in the AD pool based on the ADA assay used in the ECZTRA trials. You plan to exclude the ADA data from the Phase 2b trial (D2213C00001) for the integrated ADA evaluation and use them as supportive information based on the results from the individual CTR. Your proposal for the integrated immunogenicity evaluation of tralokinumab appears acceptable.

3.0 ADMINISTRATIVE COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

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.² 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 FDA.gov.³

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 Information⁴ and Pregnancy and Lactation Labeling Final Rule⁵ 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.

² When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

³<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>

⁴

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

⁵

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information 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*.

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS.

This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned

criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

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 items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* 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 ORA investigators who conduct those inspections. 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.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.⁶

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA.

⁶

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>
 U.S. Food and Drug Administration
 Silver Spring, MD 20993
www.fda.gov

FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

Your proposed 351(a) BLA would be within the scope of this guidance. As such, FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

4.0 ATTACHMENTS AND HANDOUTS

The sponsor provided a response to the Meeting Preliminary Comments on April 30, 2019 which is appended to the meeting minutes.

11 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KENDALL A MARCUS
05/10/2019 09:44:43 AM



IND 123797

MEETING MINUTES

MedImmune Ltd.
Attention: Annie Foster
Regulatory Affairs Director, Global Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

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 tralokinumab.

We also refer to the meeting between representatives of your firm and the FDA on September 7, 2016. The purpose of the meeting was to discuss the development plan for tralokinumab.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Strother D. Dixon, Senior Regulatory Project Manager at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Sponsor Response to Preliminary Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: September 7, 2016; 10:00 AM EST
Meeting Location: FDA, White Oak Building 22

Application Number: IND 123797
Product Name: tralokinumab
Proposed Indication: For the treatment of atopic dermatitis (AD)
Sponsor Name: MedImmune Ltd.

Meeting Chair: Kendall A. Marcus, MD
Meeting Recorder: Strother D. Dixon

FDA ATTENDEES

Julie Beitz, MD, Director, Office of Drug Evaluation III
Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Jill Lindstrom, MD, FAAD, Deputy Director, DDDP
Roselyn E. Epps, MD, Clinical Reviewer, DDDP
Hamid Tabatabai, MD, Clinical Reviewer, DDDP
Mohamed Alosch, PhD, Biostatistics Team Leader, Division of Biometrics III (DB III)
Carin Kim, PhD, Biostatistics Reviewer, DB III
Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 3 (DCP 3)
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP 3
Mishale Mistry, PharmD, MPH, Team Leader, Division of Medication Error Prevention & Analysis (DMEPA)
Matthew J. Barlow, RN, BSN, Safety Evaluator, DMEPA
Roy Blay, PhD, Reviewer, Division of Good Clinical Practices Assessment Branch
Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

EASTERN RESEARCH GROUP ATTENDEES

Marc Goldstein, Independent Assessor

SPONSOR ATTENDEES

Sarah McFarlane, B.Sc (Hons), MSc, Director Regulatory Affairs, MedImmune
Annie Foster, BS, Director Regulatory Affairs, AstraZeneca
Annette Mattsson, BSc (Pharm), Global Regulatory Lead, LEO Pharma

Doreen Morgan, PharmD, MS, Vice President, US Regulatory Affairs, LEP Pharma
Edward Piper, MD, Global Medicines Lead, AstraZeneca
Thomas Nedergaard Jensen, Project Vice President, LEO Pharma
Rene van der Merwe, MB ChB, MSc, FFPM, Senior Director, Clinical Development,
MedImmune
Millie Wang, MD, MPhil, Senior Medical Lead, Clinical Development, AstraZeneca
Bo Bang, MD, PhD, Medical Lead, LEO Pharma
Martin Jenkins, Statistical Science Director, AstraZeneca
Anita Melgaard, MSc Stat, Biostatistician Lead, LEO Pharma
Paolo Vicini, PhD, MBA, Senior Director, Clinical Pharmacology and DMPK, MedImmune
Anders Sørhoel, Clinical Pharmacologist Expert, LEO Pharma
Lotte Seiding Larsen, MSc (Pharm) Project Lead PRO Competence Center, LEO Pharma

1.0 BACKGROUND

The purpose of this meeting is to discuss the development program for tralokinumab.

2.0 DISCUSSION

2.1. Clinical Pharmacology

There were no specific Clinical Pharmacology questions submitted in the briefing package, we have the following general comments:

In your tralokinumab development program for the treatment of AD, we recommend that you conduct clinical studies in the target patient population to determine the drug-drug interaction (DDI) potential between your drug product and CYP450 substrates. We are open to further discussion regarding the clinical study design to evaluate the DDI for your product. Refer to the following guidance for more information:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>

Post-Meeting Comments:

The Sponsor provided a written response to the DDI comment which states that they are not currently planning to conduct DDI studies for tralokinumab. The Sponsor's response was not discussed at the meeting.

The Agency reiterates the recommendation in the preliminary comment.

2.2. Clinical/Biostatistics

Introductory Comments:

To date, you have conducted a Phase 2b dose-ranging study of tralokinumab in an “adjunct setting”, and you proposed to conduct two monotherapy Phase 3 trials. While the two Phase 3 trials will have some similarities in design for the induction phase, your trials will differ in the maintenance period as Study 1 will allow multiple short-course topical corticosteroids (TCS),

and Study 2 will consider those that used them as non-responders to enable assessing randomized withdrawal.

Note that for your Phase 3 trials, although you proposed the primary endpoint of the proportion of Investigator's Global Assessment (IGA) responders at Week 12, you powered your trials based on assumed IGA responder rates for Week 52.

As your Phase 2b trial was conducted in an "adjunct setting", it would be difficult to concur with your proposed induction dose of tralokinumab 300 mg SC Q2W (with or without a loading dose of 600 mg SC) along with the proposed maintenance dosing regimen (Q2W, Q4W) given the lack of preliminary efficacy and safety information in a monotherapy setting.

Question 1:

The Sponsor intends to conduct a Phase 3 program comprising (b) (4) (b) (4) Does the Agency agree that this Phase 3 package is sufficient to complete a benefit-risk evaluation for this new biological drug for the following indication: Treatment of moderate-to-severe AD in (b) (4) adults (b) (4)

Please refer to [Section 2.3.1](#) in Appendix 1 for the company position.

FDA Response to Question 1:

We have multiple issues with the trial design and analysis.

See responses to Questions 2 through 9 below.

Question 2:

Does the Agency agree with the patient population proposed by the Sponsor for the pivotal Phase 3 tralokinumab studies and the associated inclusion/exclusion criteria?

Please refer to [Section 2.3.2](#) in Appendix 1 for the company position.

FDA Response to Question 2:

For Studies 1 and 2, you have proposed the following key inclusion criteria:

- Subject age 12 to 75 years with moderate to severe AD who are candidates for systemic therapy;
- A history of TCS or TCI treatment failure in AD (due to inadequate response or intolerance) or for whom TCS or TCI are medically inadvisable;
- Screening and baseline values of AD involvement of $\geq 10\%$ body surface area;
- EASI score of ≥ 12 at screening and ≥ 16 at baseline; and
- Screening and baseline IGA score of ≥ 3 .

We have the following comments regarding study population selection:

1. Proposed study population appears reasonable.
2. Clarify treatment failure to TCS, TCI; clarify "candidate for systemic therapy".

3. You plan to evaluate the efficacy of your product on pruritus, however, you did not include baseline pruritus severity. To successfully demonstrate improvement on a symptom measure, it is important to select subjects with sufficient level of symptom severity at baseline; therefore, the inclusion criteria for your Phase 3 trials should include a threshold baseline severity for pruritus. See response to Question 5.

Meeting Discussion:

The sponsor inquired whether setting a threshold level as a success criteria can be done after the Phase 3 trials initiate and prior to unblinding of the data. In response, the Agency noted that as there is data from the completed Phase 2b study concerning the pruritus endpoint, the Agency prefers that the sponsor propose a threshold level defining success based on the information from the completed clinical studies as early as possible. Such information will help in defining the baseline enrollment criteria for the pruritus endpoint and will enable testing the endpoint along with other secondary endpoints in the multiple testing strategy. By specifying a minimum enrollment criteria based on the threshold level, this will enable all subjects enrolled in the trials to be analyzed for the pruritus endpoint which would provide more meaningful results for this endpoint.

Question 3:

Does the Agency support the rationale for the selection of the proposed dose and dose regimens for the pivotal studies? Does the Agency agree that the proposed program would lead to dose recommendations for an induction phase (single loading dose followed by Q2W dosing for 16 weeks) and a maintenance phase (Q2W or Q4W dosing)?

Please refer to Section 2.3.3 in Appendix 1 for the company position.

FDA Response to Question 3:

You proposed tralokinumab dosing regimens of 300 mg Q2W (with or without 600 mg as a loading dose) in the initial 16-week treatment period and dosing regimens of 300 mg Q2W and 300 mg Q4W in the 36-week maintenance treatment period for evaluation of tralokinumab efficacy and safety in subjects with moderate-to-severe AD across the two Phase 3 trials. We have the following comments regarding the proposed Phase 3 dosing regimens and study design at this time:

1. While the selection of 300 mg Q2W dosing regimen in the initial 16-week treatment period may be supported by the dose-response relationship for efficacy observed in your Phase 2b study (D2213C0001), risks exist in using the Phase 2b data to support Phase 3 dose selection. The Phase 2b trial was not conducted under a monotherapy setting as proposed for the Phase 3 program.
2. The patient population in the Phase 2b trial did not include adolescent patients. The similarity between adult and pediatric patients with respect to PK, PD, and dose-response/exposure-response relationships for your product is not fully understood at this time. Before you enroll adolescent subjects aged 12 and above into Phase 3 trials, you should evaluate a range of tralokinumab doses in a number of pediatric patients.

3. We are not clear about the purpose of including a treatment arm of tralokinumab 300 mg Q2W without a 600 mg loading dose in Study 2 as all other tralokinumab treatment arms in the two Phase 3 trials have a 600 mg loading dose.
4. Your Phase 2b study did not investigate the long-term tralokinumab treatment effect in AD patients. In general, dose ranging should be conducted in a manner which investigates the initial treatment phase separately from the maintenance phase because dosing for maintenance maybe different than that for the initial treatment period. We acknowledge that you have planned to include two dosing regimens (300 mg Q2W and 300 mg Q4W) in the maintenance treatment period of the Phase 3 trials; however, only one Phase 3 trial is evaluating the 300 mg Q4W regimen.
5. See introductory comments. As you conducted a Phase 2b study in an “adjunct setting”, we encourage you to conduct a Phase 2 study in a monotherapy setting to investigate the concentration, frequency of use, treatment duration to select an appropriate dose, and to get treatment effect estimates to power monotherapy Phase 3 trials.
6. The dosing regimen for dosage and administration recommendation in product labeling will be a review issue when you submit a BLA.

Meeting Discussion:

For the planned Phase 3 trials, the sponsor proposed to only enroll adult subjects and to exclude the treatment arms of 300 mg Q2W dose without the loading dose. The sponsor acknowledged that they are willing to take the risk in designing their Phase 3 trials based on data from their Phase 2b study which was conducted in an “adjunct setting”.

Question 4:

The Sponsor proposes approaches for the allowance, restriction or prohibition of concomitant background medications for AD during the Phase 3 program. Does the Agency agree that these proposals are appropriate? Does the Agency support the methods proposed for how patients taking such medications could be handled in the statistical analyses?

Please refer to Section 2.3.4 in Appendix 1 for the company position.

FDA Response to Question 4:

1. You propose to require use of basic bland emollients and 2 bleach baths per week during the first 16 weeks of Study 1 and Study 2. We agree with use of basic bland emollients during the studies. Because unbalanced use of bleach baths may affect evaluation of efficacy and safety, this treatment should not be allowed. Alternatively, you may provide your rationale for allowing such use without impacting efficacy assessment.
2. In Study 1, you propose to allow use of moderate to low potency topical corticosteroids (mild potency TCS for face, neck and intertrigo and moderate potency TCS for trunk) after Week 16, during “times of flare” on lesional skin, as needed for at most 1 week duration. We have the following comments:
 - Include criteria that will define “flare” and allow initiation of TCS therapy.

- Document number of “flares”.
 - Document type, frequency and duration of TCS use.
 - The use of multiple, non-consecutive 1-week use of rescue medication in the maintenance phase for Study 1 needs to be clinically justified. By allowing multiple, non-consecutive 1-week use of rescue medication in the maintenance phase for Study 1, you may complicate interpretation of study findings. Therefore, for interpretation of study findings in the maintenance phase, the Agency recommends that you consider those subjects that use TCS to be non-responders both during the initial treatment and the maintenance phases.
3. For Study 2 no rescue medication will be allowed following Week 16. Provide information on how subjects that experience “flares” will be managed and analyzed.
 4. In subjects requiring oral or parenteral antibiotics, antiviral, or antifungal therapy for the treatment of skin infections or other organ system infections, study drug should be held or discontinued until successful resolution of infection. Type, duration and frequency of antimicrobial therapy use should be documented.
 5. Document reason for, type, duration, and frequency of use of any topical antimicrobial agents.

Meeting Discussion:

The sponsor provided their rationale for allowing multiple, intermittent TCS use during the maintenance period of their Phase 3 trials. In response, the Agency noted that while the clinical trials can be designed for such use, handling the data for subjects with TCS use should be carried out in a meaningful way to allow proper interpretation of study findings. The sponsor should prespecify a definition/criterion for relapse as well as details about the intermittent TCS use including the TCS type, strength, frequency of application, amount, application site(s), body surface area treated, and duration of use.

Question 5:

Does the Agency agree that the endpoints described below as assessed by the indicated clinical outcome assessments can support the proposed indication and are appropriate for inclusion in the label subject to satisfactory assessment of the significance, consistency and clinical relevance? Please refer to [Section 2.3.5](#) in Appendix 1 for the company position.

FDA Response to Question 5:

You propose the primary endpoint of score of 0 or 1 and at least 2 grade reduction from baseline on 5-point IGA scale, at Week 12. The proposed IGA scale is presented below.

Table 2.3.5.1-1 IGA

0	Clear	No inflammatory signs of AD
1	Almost clear	Just perceptible erythema and just perceptible papulation / infiltration
2	Mild disease	Mild erythema and mild papulation / infiltration
3	Moderate disease	Moderate erythema and moderate papulation / infiltration
4	Severe and very severe disease	Severe erythema and severe papulation / infiltration (with or without) oozing / crusting

AD = atopic dermatitis; IGA = Investigator Global Assessment

In your proposed IGA scale, definitions for “mild,” “moderate,” “severe and very severe” lack sufficient detail to provide meaningful guidance to investigators for disease assignment to one of these levels. “Mild”, “moderate,” “severe and very severe” do not have inherent meaning in the context of morphological descriptions on the scale. Therefore, the redundancy of using the name of the level of the scale (e.g. “moderate”) to describe the level of severity of the signs (“moderate erythema”, “moderate papulation/ infiltration”) is not clinically meaningful, and the definitions require additional morphologic descriptive details to minimize inter-observer variability. Desirable features for an appropriate scale include: static, non-comparative, and limited number of categories. Each category should be distinct, non-overlapping, and represent a clinically meaningful gradation of disease severity.

You propose the following key secondary endpoints in Study 1:

- EASI 75 at Week12
- Mean weekly pruritus NRS change from baseline at Week 12.
- DLQI change from baseline at Week 12
- IGA 0 or 1 at Week 52

You propose the following key secondary endpoints in Study 2:

- EASI 75 at Week12
- Mean weekly pruritus NRS change from baseline at Week 12.
- DLQI change from baseline at Week 12
- IGA 0 or 1 at Week 12 in biomarker positive patients
- EASI 75 at Week 12 in biomarker positive patients
- IGA 0 or 1 at Week 52 among those who are IGA success at Week 16

We have the following comments regarding the proposed secondary endpoints:

1. We agree with the proposed secondary endpoint of EASI 75 change from baseline at Week 12.
2. You proposed to analyze your pruritus secondary endpoint using a mixed effects model repeated measure (MMRM); however, a mere change on the numeric rating scale (NRS) might not translate to a clinically meaningful difference. A clinically meaningful improvement in the NRS should be based on meeting a pre-specified threshold level on the NRS scale and should also be based on the proportion of subjects who meet such a threshold level.

3. All endpoints relying on PRO (pruritus, DLQI) should be validated prior to use in Phase 3 trials. Refer to the guidance for industry, *Patient –Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.
4. For comments regarding the secondary endpoints on biomarker-positive patients, see the response to Question 7.
5. You proposed the proportion of IGA responders at Week 12 as the primary endpoint, and the proportion of IGA responders at Week 52 as a secondary endpoint. Provided that the trials established efficacy at Week 12, the utility of comparing the different maintenance dosing regimens against the placebo might not be relevant as the goal of the maintenance period is not to establish an efficacy claim but to select the maintenance dose which provides higher maintenance for responders among different alternative dosing regimens.
6. Secondary endpoints intended for labeling claim should be clinically meaningful, limited in number, and adjusted for multiplicity.
7. For Study 2, you proposed that responders for entering the randomized withdrawal phase will be defined as scoring either IGA 0 or 1 or EASI 75 at Week 16. As response on the IGA scale is considered to be the primary endpoint at Week 12, we recommend criteria for responders be defined based on the IGA scale at the primary time point (i.e., Week 12).

Meeting Discussion:



The Agency reiterated the comment that the sponsor powered their Phase 3 trials using assumed response rates at Week 52 when the initial treatment phase is for 12 weeks. The Agency asked for clarification concerning the start of the maintenance period at Week 16 while the initial treatment period is 12 weeks as usually the maintenance period starts immediately following the initial treatment period. In response, the sponsor stated that the goal was to reduce bias in the Investigator's assessment. The Agency responded that the preference is to initiate the maintenance period immediately following the initial treatment period.

Question 6:

Does the agency support the proposed formulation of the hypothesis testing to be conducted in the induction and maintenance periods of the Phase 3 studies?

Please refer to [Section 2.3.6](#) in Appendix 1 for the company position.

FDA Response to Question 6:

- For Study 2, you proposed to compare pooled dose regimens vs. placebo at Week 12 first, and if statistically significant, to test each dose regimen with or without the loading dose separately at the same significance level. It should be noted that each comparison of with or without the loading dose regimen requires multiplicity adjustment to control the Type I error rate.
- You stated that “an interim efficacy analysis may be conducted” when a pre-defined proportion of subjects have evaluable Week 12 IGA response data. Your draft protocols lacked many specific details regarding the proportion of subjects for conducting the interim analysis, blinding, and the control of the Type I error rate to enable the Agency to provide comments concerning your interim analysis. It should be noted that if you plan to conduct an interim analysis, then the control of the Type I error rate will need to account for the various dose regimens, multiple endpoints, and subgroup analysis, in addition to the interim analysis.

Question 7:

If enhanced efficacy is identified in a subgroup of patients defined by a biomarker, does the Agency agree that the proposed plan would be adequate to support a label claim for a biomarker positive population?

Please refer to [Section 2.3.7](#) in Appendix 1 for the company position.



Question 8:

Does the agency agree that the Phase 3 program as outlined should provide sufficient data in patients with AD to characterize the tralokinumab benefit/risk profile, including adequate safety database exposure?

Does the agency also agree that the large safety database for asthma could also be considered as supportive data?

Please refer to [Section 2.3.8](#) in Appendix 1 for the company position.

FDA Response to Question 8:

You state that at the time of the marketing application for AD, it is anticipated that approximately 1150 subjects with AD will have been exposed to tralokinumab and 690 and 470 will have been exposed for minimum periods of 6 and 12 months, respectively. Your safety database will also include information from additional 114 healthy subjects, 1770 subjects with asthma, 138 subjects with IPF, and 55 subjects with UC.

Safety information obtained from clinical trials in different indications (asthma; IPF; UC) may be informative; however, adequate safety experience should be obtained from relevant population and from clinical trials that represent expected length of treatment, dose, and how tralokinumab will be administered for AD.

Question 9:

The Sponsor would like to introduce ‘carer/self-administration at home’ for this patient population and is considering this as an option for selected patients in Study 3 (long term extension study) who are deemed proficient and willing to follow appropriate training in the clinic setting. Does the agency have any objection to this approach?

Please refer to [Section 2.3.9](#) in Appendix 1 for the company position.

FDA Response to Question 9:

No, we do not agree with your approach from a usability perspective. We understand that you are considering caregiver and self-administration of tralokinumab for the commercial product and propose to incorporate ‘at home’ administration (either by a caregiver or self-administered by the patient) into a Clinical Use study. Based on the safety data available at the time of the application submission, you may propose ‘at home’ administration of tralokinumab. From a safety perspective, we defer the clinical team as to whether this product is appropriate for at-home administration in both the Clinical Use study and for commercialization.

With regard to the ‘at home’ administration of tralokinumab during a Clinical Use study, we recommend that that the final to-be-marketed product user interface and associated labels and labeling, including instructions for use are used in the pivotal clinical trials.

With regard to the ‘at home’ administration of tralokinumab for the commercial product, you have not submitted a comprehensive use-related risk analysis or your plans for a Human Factors (HF) validation study.

Note that a 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 (consider known problems for similar products), and the potential negative clinical consequences of use

errors and task failures. Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable. We note that there is no currently approved pre-filled syringe/drug-device combination product for the intended users and for the product's intended uses.

Based on this risk analysis, you will need to determine whether you need to perform a human factors (HF) validation study under simulated use conditions with representative users performing necessary tasks to demonstrate safe and effective use of the product. The risk analysis can be used to inform the design of a human factors validation study protocol for your product. If you determine that an HF validation study is not needed for your product, submit your risk analysis and justification for not conducting the HF validation study to the Agency for review under the IND. The Agency will notify you if we concur with your determination.

Guidance on human factors procedures to follow can be found in:

Applying Human Factors and Usability Engineering to Medical Devices, available online at: <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf>

Safety Considerations for Product Design to Minimize Medication Errors, available online at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf>

Note that we recently published two draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development can be found online at: <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf>

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors can be found online at: <http://www.fda.gov/downloads/drugs/guidancecomplianceinformation/guidances/ucm349009.pdf>

3.0 ADDITIONAL INFORMATION

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>.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for

clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission

types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

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).

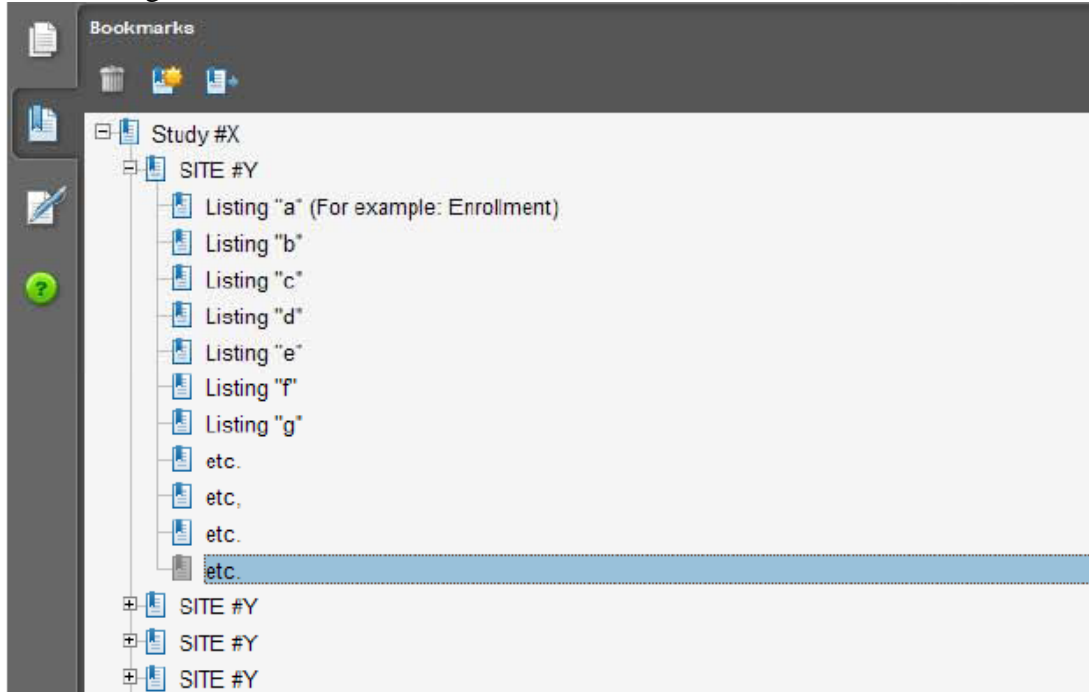
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - 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 Item¹	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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

Type B Pre-Meeting Response

Drug substance Tralokinumab

Date 6 September 2016

Tralokinumab (CAT-354)

A recombinant human mAb of the IgG4 subclass that specifically binds to human IL-13 and blocks interactions with the IL-13 receptors

Type B Pre-Meeting Response

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Based on FDA responses dated 02 September 2016, AZ/MedI believes no further clarification or discussion is needed on questions 6 or 8. We have provided a written response to the FDA's comment on the DDI study and question 9 below and request the Division's feedback on these items, either during the meeting, or if time does not allow, post-meeting responses. In response to question 5, we will provide a definition of IGA within 2 weeks, and have provided responses to some subsections of question 5, please refer to question 5 below.

Introductory Comments:

To date, you have conducted a Phase 2b dose-ranging study of tralokinumab in an "adjunct setting", and you proposed to conduct two monotherapy Phase 3 trials. While the two Phase 3 trials will have some similarities in design for the induction phase, your trials will differ in the maintenance period as Study 1 will allow multiple short-course topical corticosteroids (TCS), and Study 2 will consider those that used them as non-responders to enable assessing randomized withdrawal.

(b) (4)

Clinical Pharmacology

There were no specific Clinical Pharmacology questions submitted in the briefing package, we have the following general comments:

In your tralokinumab development program for the treatment of AD, we recommend that you conduct clinical studies in the target patient population to determine the drug-drug interaction (DDI) potential between your drug product and CYP450 substrates. We are open to further discussion regarding the clinical study design to evaluate the DDI for your product. Refer to the following guidance for more information:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>

AZ/MedI Comment:

We acknowledge that the increased use of therapeutic proteins has contributed to the concern for potential drug-drug interactions (DDIs). There have been reports of DDIs between biologics and small molecules. However, due to differing clearance mechanisms, these typically tend to be mild and are not as common as those between small molecules. We are not currently planning to conduct DDI studies for tralokinumab, for the following reasons:

- We are unaware of specific concerns that relate to modulation of IL-13, specifically with reference to the AD patient population. To date, IL-13 is not known to cause any changes in CYP enzymes in human hepatocytes. We are not aware of decrease/increase in co-administered medications in tralokinumab study patients, suggesting tralokinumab administration has no effect.
- Conversely, there has been no observed impact of co-medications on observed tralokinumab PK in asthma population PK analyses performed to date: there was no statistical difference between healthy volunteers vs. asthmatics, and by analogy any co-medication (ICS, OCS, LABA, SABA, leukotrienes) did not have an effect on tralokinumab exposure, confirming our expectation.
- Tralokinumab has an overall low immunogenicity, so other immune modulating drugs would not be expected to have an effect on tralokinumab exposure.

Given all these data together, the potential for drug-drug interactions with tralokinumab is considered low.

Can the Agency elaborate on the context for their recommendation and what safety concern needs to be addressed by the DDI study?

Question 1:

The Sponsor intends to conduct a Phase 3 program comprising 2 pivotal studies and a long-term extension study. Does the Agency agree that this Phase 3 package is sufficient to complete a benefit-risk evaluation for this new biological drug for the following indication: Treatment of moderate-to-severe AD in adolescents and adults who are candidates for systemic therapy?

FDA Response:

We have multiple issues with the trial design and analysis. See responses to Questions 2 through 9 below.

AZ/MedI Comment:

Question 1 will be discussed in relation to questions 2-7.

Question 2:

Does the Agency agree with the patient population proposed by the Sponsor for the pivotal Phase 3 tralokinumab studies and the associated inclusion/exclusion criteria?

FDA Response:

For Studies 1 and 2, you have proposed the following key inclusion criteria:

- Subject age 12 to 75 years with moderate to severe AD who are candidates for systemic therapy;
- A history of TCS or TCI treatment failure in AD (due to inadequate response or intolerance) or for whom TCS or TCI are medically inadvisable;
- Screening and baseline values of AD involvement of $\geq 10\%$ body surface area;
- EASI score of ≥ 12 at screening and ≥ 16 at baseline; and
- Screening and baseline IGA score of ≥ 3 .

We have the following comments regarding study population selection:

1. Proposed study population appears reasonable.
2. Clarify treatment failure to TCS, TCI; clarify “candidate for systemic therapy”.
3. You plan to evaluate the efficacy of your product on pruritus, however, you did not include baseline pruritus severity. To successfully demonstrate improvement on a symptom measure, it is important to select subjects with sufficient level of symptom severity at baseline; therefore, the inclusion criteria for your Phase 3 trials should include a threshold baseline severity for pruritus. See response to Question 5.

AZ/MedI Comment:

We acknowledge item 1, we will discuss items 2 and 3.

Question 3:

Does the Agency support the rationale for the selection of the proposed dose and dose regimens for the pivotal studies? Does the Agency agree that the proposed program would lead to dose recommendations for an induction phase (single loading dose followed by Q2W dosing for 16 weeks) and a maintenance phase (Q2W or Q4W dosing)?

FDA Response:

You proposed tralokinumab dosing regimens of 300 mg Q2W (with or without 600 mg as a loading dose) in the initial 16-week treatment period and dosing regimens of 300 mg Q2W and 300 mg Q4W in the 36-week maintenance treatment period for evaluation of tralokinumab efficacy and safety in subjects with moderate-to-severe AD across the two Phase 3 trials. We have the following comments regarding the proposed Phase 3 dosing regimens and study design at this time:

1. While the selection of 300 mg Q2W dosing regimen in the initial 16-week treatment period may be supported by the dose-response relationship for efficacy observed in your Phase 2b study (D2213C0001), risks exist in using the Phase 2b data to support Phase 3 dose selection. The Phase 2b trial was not conducted under a monotherapy setting as proposed for the Phase 3 program.
2. The patient population in the Phase 2b trial did not include adolescent patients. The similarity between adult and pediatric patients with respect to PK, PD, and dose-response/exposure-response relationships for your product is not fully understood at this time. Before you enroll adolescent subjects aged 12 and above into Phase 3 trials, you should evaluate a range of tralokinumab doses in a number of pediatric patients.

3. We are not clear about the purpose of including a treatment arm of tralokinumab 300 mg Q2W without a 600 mg loading dose in Study 2 as all other tralokinumab treatment arms in the two Phase 3 trials have a 600 mg loading dose.
4. Your Phase 2b study did not investigate the long-term tralokinumab treatment effect in AD patients. In general, dose ranging should be conducted in a manner which investigates the initial treatment phase separately from the maintenance phase because dosing for maintenance maybe different than that for the initial treatment period. We acknowledge that you have planned to include two dosing regimens (300 mg Q2W and 300 mg Q4W) in the maintenance treatment period of the Phase 3 trials; however, only one Phase 3 trial is evaluating the 300 mg Q4W regimen.
5. See introductory comments. As you conducted a Phase 2b study in an “adjunct setting”, we encourage you to conduct a Phase 2 study in a monotherapy setting to investigate the concentration, frequency of use, treatment duration to select an appropriate dose, and to get treatment effect estimates to power monotherapy Phase 3 trials.
6. The dosing regimen for dosage and administration recommendation in product labeling will be a review issue when you submit a BLA.

AZ/MedI Comment:

We acknowledge items 1 and 4, we will discuss items 2, 3, 5 and 7.

Question 4:

The Sponsor proposes approaches for the allowance, restriction or prohibition of concomitant background medications for AD during the Phase 3 program. Does the Agency agree that these proposals are appropriate? Does the Agency support the methods proposed for how patients taking such medications could be handled in the statistical analyses?

FDA Response:

1. You propose to require use of basic bland emollients and 2 bleach baths per week during the first 16 weeks of Study 1 and Study 2. We agree with use of basic bland emollients during the studies. Because unbalanced use of bleach baths may affect evaluation of efficacy and safety, this treatment should not be allowed. Alternatively, you may provide your rationale for allowing such use without impacting efficacy assessment.
2. In Study 1, you propose to allow use of moderate to low potency topical corticosteroids (mild potency TCS for face, neck and intertrigo and moderate potency TCS for trunk) after Week 16, during “times of flare” on lesional skin, as needed for at most 1 week duration. We have the following comments:
 - Include criteria that will define “flare” and allow initiation of TCS therapy.
 - Document number of “flares”.
 - Document type, frequency and duration of TCS use.
 - The use of multiple, non-consecutive 1-week use of rescue medication in the maintenance phase for Study 1 needs to be clinically justified. By allowing multiple,

non-consecutive 1-week use of rescue medication in the maintenance phase for Study 1, you may complicate interpretation of study findings. Therefore, for interpretation of study findings in the maintenance phase, the Agency recommends that you consider those subjects that use TCS to be non-responders both during the initial treatment and the maintenance phases.

3. For Study 2 no rescue medication will be allowed following Week 16. Provide information on how subjects that experience “flares” will be managed and analyzed.
4. In subjects requiring oral or parenteral antibiotics, antiviral, or antifungal therapy for the treatment of skin infections or other organ system infections, study drug should be held or discontinued until successful resolution of infection. Type, duration and frequency of antimicrobial therapy use should be documented.
5. Document reason for, type, duration, and frequency of use of any topical antimicrobial agents.

AZ/MedI Comment:

We acknowledge items 1 and 5, we will discuss items 2, 3 and 4.

Question 5:

Does the Agency agree that the endpoints described below as assessed by the indicated clinical outcome assessments can support the proposed indication and are appropriate for inclusion in the label subject to satisfactory assessment of the significance, consistency and clinical relevance?

FDA Response:

You propose the primary endpoint of score of 0 or 1 and at least 2 grade reduction from baseline on 5-point IGA scale, at Week 12. The proposed IGA scale is presented below.

Table 2.3.5.1-1 IGA

0	Clear	No inflammatory signs of AD
1	Almost clear	Just perceptible erythema and just perceptible papulation / infiltration
2	Mild disease	Mild erythema and mild papulation / infiltration
3	Moderate disease	Moderate erythema and moderate papulation / infiltration
4	Severe and very severe disease	Severe erythema and severe papulation / infiltration (with or without) oozing / crusting

AD = atopic dermatitis; IGA = Investigator Global Assessment

In your proposed IGA scale, definitions for “mild,” “moderate,” “severe and very severe” lack sufficient detail to provide meaningful guidance to investigators for disease assignment to one of these levels. “Mild,” “moderate,” “severe and very severe” do not have inherent meaning in the context of morphological descriptions on the scale. Therefore, the redundancy of using the name of the level of the scale (e.g. “moderate”) to describe the level of severity of the signs (“moderate erythema”, “moderate papulation/ infiltration”) is not clinically meaningful, and the definitions

require additional morphologic descriptive details to minimize inter-observer variability. Desirable features for an appropriate scale include: static, non-comparative, and limited number of categories. Each category should be distinct, non-overlapping, and represent a clinically meaningful gradation of disease severity.

AZ/MedI Comment:

We plan to provide a proposed definition of IGA within 2 weeks of the meeting and would request FDA feedback on the proposed definition.

You propose the following key secondary endpoints in Study 1:

- EASI 75 at Week 12
- Mean weekly pruritus NRS change from baseline at Week 12.
- DLQI change from baseline at Week 12
- IGA 0 or 1 at Week 52

You propose the following key secondary endpoints in Study 2:

- EASI 75 at Week 12
- Mean weekly pruritus NRS change from baseline at Week 12.
- DLQI change from baseline at Week 12
- IGA 0 or 1 at Week 12 in biomarker positive patients
- EASI 75 at Week 12 in biomarker positive patients
- IGA 0 or 1 at Week 52 among those who are IGA success at Week 16

We have the following comments regarding proposed secondary endpoints:

1. We agree with proposed secondary endpoint of EASI 75 change from baseline at Week 12.

AZ/MedI Comment:

No comment

2. You proposed to analyze your pruritus secondary endpoint using a mixed effects model repeated measure (MMRM); however, a mere change on the numeric rating scale (NRS) might not translate to a clinically meaningful difference. A clinically meaningful improvement in the NRS should be based on meeting a pre-specified threshold level on the NRS scale and should also be based on the proportion of subjects who meet such a threshold level.

AZ/MedI Comment:

The Division noted that statistical significance of mean change from baseline is not sufficient to evaluate clinical relevance for the Pruritus NRS and that a clinically meaningful improvement in the NRS should be based on meeting a pre-specified threshold level, which we acknowledge.

3. All endpoints relying on PRO (pruritus, DLQI) should be validated prior to use in Phase 3 trials. Refer to the guidance for industry, *Patient –Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

AZ/MedI Comment:

The Division also noted that all endpoints relying on PRO should be validated prior to use in Phase 3 trials which is acknowledged. To address this we plan to submit a request for a Type C meeting, where the measurement properties including a threshold level of the Pruritus NRS will be presented. Measurement properties and the threshold level will be generated on the phase 2B data, which was conducted in an ‘adjunct setting’. Does the division agree with this approach?

If in this way a Pruritus NRS threshold level is defined during the conduct of the phase 3 trials, LEO suggest to either amend the protocols or submit statistical analysis plans under the IND including a key secondary endpoint on the Pruritus NRS threshold level. Considering this change is made prior to un-blinding of the trials, would the Division accept such an endpoint as being sufficiently pre-specified in order to obtain a label claim, of course provided it is clinically meaningful and appropriate adjustment for multiplicity has been implemented?

4. For comments regarding the secondary endpoints on biomarker-positive patients, see the response to Question 7.

AZ/MedI Comment:

No comment

5. You proposed the proportion of IGA responders at Week 12 as the primary endpoint, and the proportion of IGA responders at Week 52 as a secondary endpoint. Provided that the trials established efficacy at Week 12, the utility of comparing the different maintenance dosing regimens against the placebo might not be relevant as the goal of the maintenance period is not to establish an efficacy claim but to select the maintenance dose which provides higher maintenance for responders among different alternative dosing regimens.

AZ/MedI Comment:

To be discussed at meeting

6. Secondary endpoints intended for labeling claim should be clinically meaningful, limited in number, and adjusted for multiplicity.

AZ/MedI Comment:

No comment

7. For Study 2, you proposed that responders for entering the randomized withdrawal phase will be defined as scoring either IGA 0 or 1 or EASI 75 at Week 16. As response on the IGA scale is considered to be the primary endpoint at Week 12, we recommend criteria for responders be defined based on the IGA scale at the primary time point (i.e., Week 12).

AZ/MedI Comment:

To be discussed at meeting, if time allows

Question 6:

Does the agency support the proposed formulation of the hypothesis testing to be conducted in the induction and maintenance periods of the Phase 3 studies?

FDA Response:

For Study 2, you proposed to compare pooled dose regimens vs. placebo at Week 12 first, and if statistically significant, to test each dose regimen with or without the loading dose separately at the same significance level. It should be noted that each comparison of with or without the loading dose regimen requires multiplicity adjustment to control the Type I error rate.

- You stated that “an interim efficacy analysis may be conducted” when a pre-defined proportion of subjects have evaluable Week 12 IGA response data. Your draft protocols lacked many specific details regarding the proportion of subjects for conducting the interim analysis, blinding, and the control of the Type I error rate to enable the Agency to provide comments concerning your interim analysis. It should be noted that if you plan to conduct an interim analysis, then the control of the Type I error rate will need to account for the various dose regimens, multiple endpoints, and subgroup analysis, in addition to the interim analysis.

AZ/MedI Comment:

We acknowledge your comment and will provide appropriate details in the clinical protocol.

Question 7:

If enhanced efficacy is identified in a subgroup of patients defined by a biomarker, does the Agency agree that the proposed plan would be adequate to support a label claim for a biomarker positive population?

FDA Response:

You plan to use surrogate (pathophysiologic) biomarkers to support a labeling claim. Only results of surrogate endpoints that are pre-specified and validated can be used in support of labeling claims provided that the hypotheses are specified along with the statistical method for analysis. Further, the statistical methods for testing need to control Type I error rate, and

replication of study findings are needed to establish efficacy claim. Simple correlation between the surrogate and the “direct” endpoint, no matter how strong, is not sufficient to establish validity of such an endpoint.

AZ/MedI Comment:

We would like to clarify the plan for using biomarker data to support a label claim relating to increased levels of efficacy in a biomarker-defined subgroup. We are proposing a structured approach to precisely define biomarker sub-populations before formally testing hypotheses relating to the primary and key secondary endpoints in an independent study, with procedures for the control of type I error specified prior to unblinding. There is no intention to use biomarkers as surrogate endpoints or to rely purely on correlations to support claims.

We recognize the need to provide replication. Our proposals build on findings from the phase 2b study, seek to refine the precise definition of sub-populations in a further phase 3 study and then to formally confirm these findings in a third study. Given this process of building evidence over 3 studies in a structured way we would suggest that persuasive evidence of replication would be generated.

Since the meeting request was submitted to the division there has been the release of an FDA draft guidance on “principles for co-development of an in vitro companion diagnostic device with a therapeutic product”. Although we envisage a complementary rather than companion diagnostic, this appears relevant and we believe that our plans are in keeping with the spirit of this draft guidance. The draft guidance recognizes the difficulty of confirming a cutoff in a continuous marker and that analyses of a range of cutoffs may be needed initially (lines 839-842), suggesting that where the optimal cutoff be unknown before data are available in sufficient subjects the findings could be confirmed in a subsequent trial with a new cutoff (lines 983-987).

Our plans allow us to pre-specification of several aspects including:

- The primary analysis endpoints
- The sampling procedures
- The assays to be used
- The statistical analysis methods

We however seek the opportunity to learn more about two aspects:

- The selection of the optimal marker between the specified candidates of DPP-4 or periostin
- The ability to refine the cutoff thresholds.

Could the division advise on whether one of these two aspects is the primary source of the stated concerns?

Question 8:

Does the agency agree that the Phase 3 program as outlined should provide sufficient data in patients with AD to characterize the tralokinumab benefit/risk profile, including adequate safety database exposure?

Does the agency also agree that the large safety database for asthma could also be considered as supportive data?

FDA Response:

You state that at the time of the marketing application for AD, it is anticipated that approximately 1150 subjects with AD will have been exposed to tralokinumab and 690 and 470 will have been exposed for minimum periods of 6 and 12 months, respectively. Your safety database will also include information from additional 114 healthy subjects, 1770 subjects with asthma, 138 subjects with IPF, and 55 subjects with UC.

Safety information obtained from clinical trials in different indications (asthma; IPF; UC) may be informative; however, adequate safety experience should be obtained from relevant population and from clinical trials that represent expected length of treatment, dose, and how tralokinumab will be administered for AD.

AZ/MedI Comment:

No comment

Question 9:

The Sponsor would like to introduce ‘carer/self-administration at home’ for this patient population and is considering this as an option for selected patients in Study 3 (long term extension study) who are deemed proficient and willing to follow appropriate training in the clinic setting. Does the agency have any objection to this approach?

FDA Response:

No, we do not agree with your approach from a usability perspective. We understand that you are considering caregiver and self-administration of tralokinumab for the commercial product and propose to incorporate ‘at home’ administration (either by a caregiver or self-administered by the patient) into a Clinical Use study. Based on the safety data available at the time of the application submission, you may propose ‘at home’ administration of tralokinumab. From a safety perspective, we defer the clinical team as to whether this product is appropriate for at-home administration in both the Clinical Use study and for commercialization.

With regard to the ‘at home’ administration of tralokinumab during a Clinical Use study, we recommend that that the final to-be-marketed product user interface and associated labels and labeling, including instructions for use are used in the pivotal clinical trials.

With regard to the ‘at home’ administration of tralokinumab for the commercial product, you have not submitted a comprehensive use-related risk analysis or your plans for a Human Factors (HF) validation study.

Note that a 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 (consider known problems for similar products), and the potential negative clinical consequences of use errors and task failures. Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable. We note that there is no currently approved pre-filled syringe/drug-device combination product for the intended users and for the product's intended uses.

Based on this risk analysis, you will need to determine whether you need to perform a human factors (HF) validation study under simulated use conditions with representative users performing necessary tasks to demonstrate safe and effective use of the product. The risk analysis can be used to inform the design of a human factors validation study protocol for your product. If you determine that an HF validation study is not needed for your product, submit your risk analysis and justification for not conducting the HF validation study to the Agency for review under the IND. The Agency will notify you if we concur with your determination.

Guidance on human factors procedures to follow can be found in:

Applying Human Factors and Usability Engineering to Medical Devices, available online at: <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf>

Safety Considerations for Product Design to Minimize Medication Errors, available online at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf>

Note that we recently published two draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development can be found online at: <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf>

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors can be found online at: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

AZ/MedI Comment:

We would like to clarify our intent with home-use. Our intent is to do the risk analyses according to the FDA guidance document with the to-be-marketed product. Based on the outcome of those results we will consider whether a HF study is warranted. If an HF study is warranted, we

consider engaging with the Agency to discuss key elements of the study. However we would like to clarify the following point; are the proposed number of patients (140) in the long-term extension study, planned to be provided in the BLA, considered to be sufficient by the Agency?

In addition, we would like to get clarity on the statement in the Preliminary meeting communication (Lines 333-335) about the relevance for at-home administration. Can the clinical team provide feedback on what safety elements are needed in order to proceed with at-home administration in both the Clinical Use study and for commercialization?

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

/s/

KENDALL A MARCUS
09/09/2016