DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville P ke
Rockville, MD 20852-1448

MID-CYCLE MEETING SUMMARY

To:	The File
Date and Time:	July 10, 2013, 11:00 am – 1:00 pm
Summary:	Review of Mid-cycle progress
STN #:	125473.0
Submission Type:	Biologics License Application (BLA), Original Submission (OS)
Applicant:	Merck Sharp & Dohme Corp.
Product:	GRASTEK, Timothy Grass (*Phelum pratense*) Pollen Allergen Extract
Meeting Chair:	CAPT Jon Daugherty, PhD
Meeting Recorder:	Rana Chattopadhyay, PhD
Signature:	

CBER/FDA Attendees

CAPTJon Daugherty, PhD
Jennifer Bridgewater, MPH
Ronald L. Rabin, MD
Nabil Al-Humadi, PhD
Cherry Geronimo, BS
Erica Giordano, CSO
Tammy Massie, Ph.D.
Loris McVitte, PhD
Daphne Stewart, CSO
Jay Slater, MD
Patricia Holobaugh, PhD
Wellington Sun, MD
Philip Krause, MD
Karen Farizo, MD
William McCormick, PhD
LCDR Juan Lacayo, PhD
Rana Chattopadhyay, PhD
Steven Kunder, PhD
Taruna Khurana, PhD
Deborah Trout, CSO
Kristine Khuc, PharmD
Patricia Rohan, MD
Julienne Vaillancourt, RPh, MPH
Paul Richman, PhD
Carolyn Renshaw, PhD
Robert Fischer, MSN., RN
Marion Gruber, PhD
Theresa Finn, PhD
Katie Rivers, MS
CAPT Colleen Sweeney, RN, MS

1.0 PURPOSE

To discuss the milestones, review progress to date and any significant review issues identified with management.

2.0 BACKGROUND

***IND Phase*:**

Merck, in collaboration with ALK-Abelló A/S, Horsholm, Denmark, is developing a novel oral pharmaceutical formulation of the allergen extract from Timothy Grass (*Phleum pratense*) pollen in tablet form (MK-7243) for sublingual oral administration for the treatment of grass pollen induced allergenic rhinitis, with or without conjunctivitis. Merck proposes an indication for disease modifying treatment of grass-pollen-induced rhinitis and conjunctivitis in adults and children (5 years of age (b)(4)), who are sensitized to Timothy and related grasses, determined by specific testing (IgE) and with a history of symptoms during grass pollen season.

The clinical development plan for MK-7243 includes Five Phase 1 safety trials conducted in Europe, not under U.S. IND, (GT-01, GT-03, and GT-04 in adults; GT-09 and GT- 11 in children); one Phase 2 safety and efficacy trial conducted in Northern Europe and Canada, not under U.S. IND, (GT-07); one dose-finding Phase 2/3 efficacy and safety trial conducted in Europe, not under U.S. IND, (GT-02); and six Phase 3 efficacy trials (GT-08 in adults conducted in Europe not under U.S. IND, GT-12 in children, conducted in Germany, not under U.S. IND.

Phase 3, randomized, placebo controlled, parallel-group, double-blind studies of Timothy Grass (*Phleum pratense*) oral tablet (SCH 697243) in subjects with a positive skin prick test (SPT) lgE against *Phleum pratense* and a history of grass pollen induced rhinoconjunctivitis, with or without asthma, conducted under U.S. IND 13143, include Studies GT-14 and P05238 in adults conducted in North America; Study P05239 in children conducted in Germany and North America, respectively; and Study P08067 in both adults and children conducted in North America.

***Pre-BLA (Type-B) Meeting Phase*:**
On November 12, 2012, CBER received a request for a Type B pre-BLA meeting from Dr. Scott Greenfeder, Merck Sharp & Dohme Corp., (Merck), to discuss data from the completed clinical development program of Timothy Grass (*Phleum pratense*) pollen extract in tablet form (MK-7243), prior to filing a BLA submission. The meeting request was deemed acceptable. Merck submitted a pre-BLA meeting briefing package on December 7, 2012. On January 9, 2013, CBER sent its response to the sponsor's questions in the pre-BLA briefing package. A Type-B meeting (teleconference) with the sponsor took place on January 10, 2012, a summary of which was sent to the sponsor on February 07, 2012.

***BLA Submission Phase*:**
BLA STN # 125473.0 was submitted by Merck Sharp & Dohme Corp. on January 25, 2013 and received by CBER on January 25, 2013, for GRASTEK [Timothy Grass (*Phleum pratense*) Pollen Allergen Extract] sublingual tablet for the treatment of diagnosed Timothy and related grass pollen induced allergic rhinitis, with or without conjunctivitis in adults and children 5 years of age and older.

2.1 Review Committee
The review committee is as follows:

CAPT Jon Daugherty, PhD	Chairman
Rana Chattopadhyay, PhD	Regulatory Project Manager
LCDR Juan Lacayo, PhD	Regulatory Project Manager
Ronald Rabin, MD	Clinical Reviewer
Taruna Khurana, PhD	Product Reviewer (DBPAP)
Cherry Geronimo, BS	Product/Lot Testing (DBPAP)
Jennifer Bridgewater, MPH	Regulatory Coordinator (DBPAP)
Steven Kunder, PhD	Toxicology Reviewer
Nabil Al-Humadi, PhD	Toxicology Reviewer
Deborah Trout, CSO	CMC/Facility Reviewer (DMPQ)
Erica Giordano, CSO	Lot Release testing/Protocol
James Kenney, CSO	DBSQC Reviewer
Kristine Khuc, PharmD	Labeling Reviewer (APLB)
Tammy Massie, PhD	Biostatistics Reviewer
Patricia Rohan, MD	Epidemiology Reviewer
Lillian Ortega, CSO	BiMo Reviewer

David Schwab, CSO Electronic Integrity Reviewer

2.2 Milestones & Meetings [Gray out completed milestones]

MILESTONES:

Submitted: January 25, 2013
Received: January 25, 2013
Committee Assignment: February 08, 2013
First Committee Meeting: February 15, 2013
Filing Meeting: March 11, 2013
Filing Action: March 26, 2013
Deficiencies Identified: April 7, 2013
APAC Determination: April 10, 2013
PeRC Determination: June 9, 2013
First Draft Reviews Due: April 25, 2013 [Statistical & Pharmacovigilence review draft was due by May 25, 2013]
Second Draft Reviews Due: July 19, 2013 [Statistical & Pharmacovigilence review draft is due by August 3, 2013]
Final Reviews Due: December 11, 2013.
Action Due: January 25, 2014
Action Package for Posting Due: January 25, 2013.

MEETINGS:

First Committee Meeting: March 6, 2013
Filing Meeting: March 6, 2013
Monthly Team Meetings: April 10, 2013; May 6, 2013; June 7, 2013
Mid-Cycle Review Meeting: July 10, 2013
PeRC: October 23, 2013
APAC: November 5 & 6, 2013
Labeling Meetings: July 31, 2013

2.3 Information Requests

Date	***Summary***
April 2, 2013	IR regarding manufacturing, facility and microbiology testing
April 9, 2013	IR regarding location of statistical data set in the OS

2.4 Amendments

Amendment Number	Description	Date of Cover Letter
Original Submission	BLA Submission [STN 125473.0]	January 25, 2013
001	Statistical Information	April 25, 2013

002	Partial Response to IR, dated 04/02/2013	May 3, 2013
003	Packaging component labeling changes based on CBER proposed proper name of the product and dosage form.	May 22, 2013
004	Response to IR, dated 04/02/2013	May 24, 2013

2.5 Relevant Telecons (including E-Mail Communications)/Decisions

Teleconference	Description	Date
001	UNII Codes communicated to the sponsor	March 29, 2013
002	**Information Request** regarding the location of the statistical efficacy data set.	April 9, 2013
003	**Advice:** In response to sponsor's query through e-mail, the sponsor is notified that 120 day safety update can be submitted to BLA [STN 125473.0]. For submitting ongoing spontaneous reporting of adverse events in Europe, sponsor may follow the same format which they use to provide the information to the European regulatory authority. For ongoing non-IND studies, CBER prefers that the safety update be submitted in tabular format. CBER determined that the cut-off date for this report is April 30, 2013 and the sponsor will have to submit it to its BLA (STN 125473.0) no later than June 30, 2013.	May 2, 2013
004	**Advice:** In response to sponsor's e-mail regarding submission of information supporting the efficacy of MK-7243 against grass cross-reactive to Timothy Grass, the sponsor is advised to first submit the information informally for CBER review to determine its relevance to the BLA.	May 20, 2013

3.0 DISCUSSION TOPICS: STATUS AND ISSUES

3.1 Product

Dr. Taruna Khurana presented the status of her review of Drug substance (DS) and Drug Product (DP) sections. Review of batch production and master record are pending. She anticipates that primary review will be completed by end of August 2013. There is a pending response from the sponsor to an information request, dated June 18, 2013, on measurement of (b)(4) unit by (b)(4) for the final DP release testing. Dr. Khurana observed that the 'source material' section in the BLA is brief, certificate of analysis provided by (b)(4), has indicated multiple SOPPs but none of these SOPPs are included in this BLA. There is also no data about the stability testing on the source material. There was a discussion, involving Dr. Philip Krause, Dr. Theresa Finn, Dr. Jay Slater and Dr. Paul Richman, regarding the requirement of having either all information on source materials for drug product in the BLA or having a cross-reference letter for the use of Master File from (b)(4) the sponsor of the Master File for the source materials. At the end of the discussion, Dr. Richman and Dr. Slater concluded that generally allergenic products licensees declare the origin

of the source materials and tests performed on the source materials. Dr. Marion Gruber suggested that if the Master File from (b)(4) (related to this BLA) described the processing of the source materials for drug product, it is acceptable and no further information is required on that issue from the sponsor of the BLA. Dr. Richman and Dr. Slater concurred with this suggestion.

[NOTE: *CAPT Colleen Sweeney clarified that* (b)(4) *is the sponsor of the Master File for the 'Source Material' and Merck later on purchased* (b)(4) **].**

3.2 Inspection

Ms. Deborah Trout reconfirmed her initial assessment to waive the inspections for all three sites (two sites in Denmark and one site in UK) involved with the product development for this BLA as those sites were inspected by FDA between November 2011 and December 2012.

3.3 Testing

Dr. Rana Chattopadhyay (in absence of CDR James Kenney, DBSQC/OCBQ/CBER) informed the committee that the microbiological enumeration testing review for the product under this BLA is completed and CDR Kenney has uploaded his final review memo in the EDR.

Ms. Jennifer Bridgewater mentioned that determination of tests for lot release is pending and she, along with Taruna Khurana, Cherry Geronimo and Erica Giordano, will work on that.

3.4 Pre-Clinical/Toxicology

Dr. Steven Kunder mentioned that so far he did not identify any major issue in his review of the reproductive toxicology and genotoxicity study reports. He wanted a clarification about any correlation between the two unitages, BAU and SQ-T. Dr. Ronald Rabin and Dr. Jay Slater explained it to him and Dr. Rabin agreed to forward him relevant literature on this.

Dr. Nabil Al-Humadi did not observe any major issue in the results of the pre-clinical studies in rabbits and dogs other than reduced T, B and NK responses. However, those data are not from any animal study using SLIT**. Dr. Rabin mentioned that he will look the clinical study data for any reduction in those immune components. ** [**NOTE**: *After the meeting Dr. Nabil Al-Humadi confirmed that the sub-lingual route was used to administer the product in pre-clinical studies but not in tablet form but in liquid form*].

3.5 Clinical

Dr. Ronald Rabin said that almost 40% of his review is completed and he is expecting to complete his primary review by August 01, 2013. He explained the outline of all clinical studies included in the BLA. So far he did not identify any key findings that are inconsistent with the general conclusion that the product is safe and effective for the treatment of allergy to Timothy Grass pollen.

Dr. Rabin mentioned that Dr. Hendrick Nolte from Merck called him on July 09, 2013 to discuss the clinical indication for GRASTEK. Dr. Nolte stated that it is not the sponsor's intention to state that the product offers cross-reactivity to other grass pollen allergens, only that the indication is not limited to Timothy grass mono-allergic patients. In response, Dr. Rabin stated that he did not believe it was the agency's attempt to limit the indication to Timothy mono-allergic patients.

With regard to the sponsor's assertion that the product may indeed be effective for treating allergies to grass pollens other than Timothy, he stated to Dr. Nolte that the sponsor would have to make that case to the agency as one that is separate and distinct from the patient population

that may benefit from GRASTEK and serologic data will not support such assertions, and may not be included in the PI. Essentially, the sponsors will have to perform clinical studies to demonstrate such benefit, and those studies must have clinical endpoints relevant to allergic rhinoconjunctivitis (i.e. skin testing will not be sufficient).

3.6 Statistical
Dr. Tammy Massie explained that almost 30% of her review is completed and so far the results she has reviewed appear to be reasonable and meaningful. She will continue with her review and data analysis.

3.7 BiMo
Dr. Patricia Holobaugh presented the status of BiMO review for this BLA as the assigned reviewer, Ms. Lillian Ortega was on leave. BiMO is inspecting five sites in the USA and one site in Canada related to the clinical studies for this BLA. All of these inspections will be completed by August 2013 and then BiMO will submit the final report to the review committee.

3.8 Proprietary Name/Labeling
Ms. Kristine Khuc mentioned that Proprietary Name for the product has already been accepted. She observed lots of 'promotional' terms used in the labeling which needs to be discussed during the labeling meetings.

Dr. Rabin clarified that "disease modifying treatment" as mentioned under the proposed indication, is not an endpoint of any clinical study and CBER already mentioned that to the sponsor indicating that term should not be part of the indication.

3.9 Epidemiology/Post-marketing/REMS
Dr. Patricia Rohan did not identify any issue, so far, in her review of the epidemiology/post-marketing data and the recently submitted safety update report covering period from October 01, 2012 to April 30, 2013.

3.10 Advisory Committee & PeRC
Dr. Rana Chattopadhyay confirmed with Mr. Robert Fischer that the PeRC for this BLA is scheduled for October 23, 2013. Mr. Fischer and Dr. Rabin will finalize the required paperwork for PeRC.

Dr. Chattopadhyay mentioned that the Advisory Committee (APAC) meeting in which this BLA will be presented is scheduled for November 5-6, 2013. He confirmed with Ms. Katie Rivers regarding the APAC Planning meeting scheduled for July 30, 2013.

3.11 Carton, Container/Labeling
Dr. Rana Chattopadhyay mentioned that internal meetings on Labeling will be scheduled after the mid-cycle meeting.

3.12 Labeling Review Plan
See comments under section 3.11 above

3.13 Final Action Status
Review of the BLA will continue.

4.0 CONCLUSION

4.1 Most discipline reviewers are so far almost in the half way of their review except the microbiological testing review, which is completed.
4.2 No major issue has been identified in the review of the BLA, so far, by any reviewers.
4.3 Outstanding issues include response from the sponsor on measurement of (b)(4) unit by (b)(4) for the final DP release testing, decision on acceptability of 'cross-reactive' efficacy of this product with other grass-pollen allergens and 'disease modifying treatment' and other promotional terms in the labeling.

5.0 SUMMARY OF ACTION ITEMS

5.1 Dr. Ronald Rabin will provide literature to Dr. Steven Kunder on relationship between BAU and SQ-T units.
5.2 Dr. Rabin will look into the clinical immunology data and let Dr. Nabil Al-Humadi know if any reduction in T-cell, B-cell and NK-cell populations is observed.
5.3 Dr. Rana Chattopadhyay will write the summary of this meeting.