



Memorandum

Date February 09, 2017

From Wellington Sun, M.D.
Director, Division of Vaccines and Related Products Applications (DVRPA)

Subject BLA Supplement: STN 125592 Toxicology Review of House Dust Mite Allergen Extract

To Marion F. Gruber, Ph.D.
Director, Office of Vaccine Research and Review (OVRR)

Background: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (the Applicant) submitted a Biologics License Application (BLA), STN 125592 on February 9, 2016, for licensure of House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract. The proprietary name is ODACTRA™ and the dosage form for this product is a tablet for sublingual use. ODACTRA is an allergen extract indicated as immunotherapy for the treatment of house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis, confirmed by *in vitro* testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites, or skin testing to licensed house dust mite allergen extracts. ODACTRA is proposed for use in adults 18 through 65 years of age.

The Applicant submitted as part of the BLA a reproductive toxicology study (P120737) in mice which was reviewed by Dr. Ching-Long Sun. The study was titled: Subcutaneous dose study for effects of mixture of *Dermatophagoides farinae* and *Dermatophagodes pteronyssinus* allergen extract on embryo-fetal development in mice. Details of the study as described in the Toxicology review:

Performing laboratory: (b) (4)
Initiation date: February 25, 2013
Final Report date: November, 8, 2013
Test article batch/lot: 121-256
Animal species and strain: (b) (4)
Breeder/supplier: (b) (4)
Number of female animal per group: 22
Age: 10-11 weeks
Average body weight: 23-32 g
Route and site of administration: Subcutaneous; back

Volume of injection: 10 ml/kg (0.23-0.32 ml/animal)

Frequency of administration and study duration: Daily on gestation days (GDs) 6-17; 1 month

Dose: 450, 900, or 1800 DU/kg or 12.5, 25, or 50 DU/animal

Stability: The dosing formulations (45, 90 and 180 DU/mL) had been confirmed to be stable as described in supplement 1 for (b) (4) and in supplement 2 for (b) (4)

Means of administration: A syringe with a 26G needle

Experimental Design

Group	Test article	Dose DU/kg	Dose DU/animal	Dosing volume ml*	No. of animals	Number of pregnant animals	No. of Cesarean
1	Control	0	0	0.28	22	19	19
2	Low	450	12.5	0.28	22	17	16**
3	Mid	900	25	0.28	22	20	20
4	High	1800	50	0.28	22	20	18**

Evaluated parameters

Parameters	Frequency of Testing
Mortality and clinical observations	Twice daily during dosing period and daily during other times
Body weight	GDs 0, 2, 4, 6, 8, 10, 12, 14, 16 and 18
Food consumption	GDs 1, 2, 4, 6, 8, 10, 12, 14, 16 and 18
Scheduled maternal euthanasia for numbers of corpora lutea, implantations, early resorptions, late resorptions, dead/live fetuses, placenta and external anomalies	GD 18
Scheduled fetal euthanasia skeletal (1/2 litters) and visceral (1/2 litters) Examinations in control and high-dose Groups only	GD 18

The results as reported in the Toxicology review (pg. 14):

Dams

Mortality: One animal in low dose group died on GD 15. This animal was necropsied and no abnormalities were macroscopically observed at the necropsy. The death was judged not to be treatment-related, since it was not dose-dependent. Additionally, this animal was non-pregnant. Therefore, the data obtained from this animal was excluded from the evaluation. All other mice survived to scheduled euthanasia.

Pregnancy: There were 3, 5, 2, and 2 non-pregnant animals in groups 1, 2, 3 and 4 respectively.

Delivery: One and two dams in groups 2 and 4, respectively, had early delivery before the scheduled necropsy on GD18. The body weight, food consumption on GD 18 and cesarean sections from these animals were excluded.

Clinical signs: No findings were observed at any dose level.

Body weights: No differences in body weights were observed.

Food consumption: Food consumption was unaffected except a slight transient increase on GD8 in high-dose group.

Necropsy: No organs or tissues were preserved for microscopic examination since no gross findings were observed.

Fetuses

Number of corpora lutea, implantations, pre-implantation losses, post-implantation losses, live fetuses, sex ratio, and body weights of the live fetuses: There were no treatment-related changes except the percent of late resorption was increased at low dose group (2.48%) and mid-dose group (4.77%) vs 0.44% in control group. However the incidences were within the historical control data range of 0-6.02% at the testing facility as provided in amendment 2 and the findings were considered to be incidental.

Visceral examinations: No abnormalities or variations were observed.

Skeletal examinations: The incidence of fused sternbrae was observed in 2 of 105 fetuses (1.9%) or 2/18 litters in control group and 4 of 104 fetuses (3.9%) or 4/18 litters in high-dose group. The incidence in fetuses was above the upper limit of the historical data at the test facility (2/140 fetuses, 1.4%, 4 studies, 2003-2013). Therefore this skeletal malformation finding was considered to be test article-related by the Toxicology reviewer. The progress of ossification of sacrocaudal body was lower (11.857) in high-dose group. However, the incidence was around the upper limit of historical data at the testing facility (11.609, 4 studies, 2003-2013). This finding was not considered to be test article-related.

GLP study deviations or amendments: There were neither deviations from the study protocol nor unpredicted events.

Toxicology reviewers Assessment: There were no test article-related effects on clinical signs, body weight, and food consumption in dams. There were no visceral anomalies and variations. However, an increased incidence of fused sternbrae was observed in high-dose group above the historical control incidence range. This finding should be described in section 8.1 of the Prescribing Information (PI).

Discussion: There was disagreement among the review team on whether this finding of fused sternbrae in the murine reprotoxicology study merited description in the Section 8.1 of the PI as stated in the review assessment, also signed off by the Toxicology supervisor Dr. Martin Green. The Toxicology perspective is to report the abnormal findings as presented. However in order to interpret the finding it would be important to assess if there is a dose-relationship but only the findings in the highest group was reported. Clinical reviewer and Chair are taking a different approach to the animal data by using a measure of clinical judgment in interpreting if the finding is likely to be a potential safety signal. Considerations were given to the fact that the finding was

isolated in the absence of other skeletal findings and that the difference in numbers was only 2 animals out of a denominator of 100 animals (4/104 or 3.9% in High-dose group to 2/105 or 1.9% in Controls). The clinical reviewer also considered the long history of the safety of subcutaneous immunotherapy with HDM in humans without any known increase in teratogenicity. In addition to these considerations by the clinical reviewer and her supervisors it should be pointed out that the rate of fused sternbrae in the control group of this study (1.9%) is also above the historical range (1.4%) for the testing facility. Furthermore, there is at least one prospective study of HDM immunotherapy in 155 pregnant women with duration of follow-up of 6 years that did not show any increase in congenital anomalies compared to controls of pregnant women treated with steroids (Shaikh WA and Shaikh SW *Eur J of Allergy and Clin Immunology* 2012 67:741-3). Taken together it is reasonable to conclude that the isolated finding of fused sternbrae in a single murine study does not represent a potential safety signal for HDM-related congenital adverse outcome in pregnant women.

Recommendations:

Study P120737 result of isolated fused sternbrae does not in itself constitutes a potential safety signal. The isolated finding of fused sternbrae in only 2 additional mice should be evaluated in the context of the limitations of the reprotoxicity study and what is known about the safety of HDM immunotherapy in humans. I concur with not including the finding under *Animal Data* in Section 8.1 of the PI because it would inappropriately communicate an elevated risk in pregnant women that is difficult to justify based on this finding.