2 SYNOPSIS

Name of Sponsor/Company: DBV TECHNOLOGIES	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: DBV712 Peanut Allergy Vaccine (or Viaskin® Peanut)	Volume:	
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Title of Study: Epicutaneous Immunotherapy (EPIT) for Peanut Allergy: A Randomized, Double-Blind, Placebo-Controlled Phase 1 Safety Study in Adult and Pediatric Subjects

Investigators: Five investigators in the United States participated in this study: PPD

Study Centers: The study was conducted at 5 investigative centers in the United States.

Study Period: First subject, first visit (for nonsevere): 21 July 2010 Last subject, last visit (for nonsevere): 22 June 2011 First subject, first visit (for severe): 31 Jan 2011 Last subject, last visit (for severe): 27 Feb 2012	**Phase of Development:** 1b

Objectives: The primary objective was to assess the safety and tolerability of repeated applications of DBV712 in adults, adolescents, and children with known allergy to peanut. The secondary objectives were to evaluate the safety of DBV712 by measuring the proportion of subjects who experienced and required a treatment for systemic reactions related to DBV712 and to evaluate the overall adherence to the study treatment.

Methodology: This was a Phase 1, randomized, double-blind, placebo-controlled safety study conducted using 3 age groups of subjects (adults, adolescents, and children) randomized sequentially (adults first, adolescents second, and children last) to DBV712. Four (4) different doses of peanut protein per patch (20 µg, 100 µg, 250 µg, and 500 µg) and 2 different dosing regimens (1 Viaskin patch every 24 hours or 1 Viaskin patch every 48 hours) were investigated during a 2-week treatment period.

The study included 2 populations of peanut-allergic subjects (nonsevere and severe subjects). The nonsevere subjects were those with a history of allergy to peanuts with anaphylaxis reactions grade ≤3 and the severe subjects were those with a history of allergy to peanut with anaphylaxis reactions of grade 4 or 5. The severe subjects were all adults.

The study consisted of cohorts of 5 subjects. In each cohort, subjects were randomized in a 4:1 ratio (DBV712: placebo). In each cohort, a minimum of 3 of the 5 subjects were randomized at a single site.

This study included 3 periods for each subject: a Screening Period; a Treatment Period with outpatient visits at Day 1, Day 2, Day 3, Day 8/9 (depending on treatment regimen), and Day 15; and a Follow-up Period consisting of a visit 7 days after dosing was completed.

A total of 22 cohorts were planned.

To start the study, 8 cohorts of 5 adults (40 nonsevere adults) were planned to be treated, followed by 4 cohorts of 5 adolescents (20 nonsevere adolescents), then 4 cohorts of 5 children (20 nonsevere children), all with a history of anaphylaxis reactions to peanut of grade ≤3. This was to provide a total of 80 nonsevere subjects.

After the initial 8 cohorts of nonsevere adults (40 adults) were treated safely, then 6 cohorts of 5 severe peanut allergic adults with history of anaphylaxis reactions to peanut of grade 4 or 5 (30 adults) were to be treated.

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This study began with the oldest of the 3 sequential age groups: Ages 18 to 50 years (adults). Each of the 4 doses of DBV712 was tested sequentially using both the 1 application of Viaskin patch every 24-hour regimen and the 1 application of Viaskin patch every 48-hour regimen. A total of 8 cohorts of 5 adults (40 nonsevere adults), all with a history of anaphylaxis reactions to peanut of grade ≤3, were randomized. All cohorts were treated for a 2-week treatment period. The independent DSMB reviewed safety data for all subjects at a dose level before deciding on escalation to the next dose. This process was repeated until the maximum dose was reached in the adult population.

After the maximum tolerated dose in the nonsevere adults was determined, 2 cohorts of nonsevere adolescents (aged 12 to 17 years) were evaluated using both dosing regimens at the dose below the maximum tolerated adult dose (250 µg was planned). The independent DSMB reviewed safety data for all subjects at this dose level before deciding on escalation to the next dose. Two more adolescent cohorts were enrolled using both dosing regimens at the maximum tolerated adult dose (500 µg was planned). The 4 adolescent cohorts had to complete their 2 weeks of treatment, and a review of the safety data had to be made before the child cohorts could be enrolled.

Study accrual continued in nonsevere children (aged 6 to 11 years). Four child cohorts were to be enrolled and treated using a similar paradigm as for the adolescent cohorts, starting with evaluation of 2 cohorts using both dosing regimens at the dose below the maximum tolerated adolescent dose (250 µg was planned) prior to escalating to the higher dose (500 µg was planned). Severe adult subjects with a history of anaphylaxis reactions of grade 4 or 5 (who experienced dyspnea, cyanosis, hypoxia, hypotension, and/or neurological compromise) were to be treated only after safety was assessed as satisfactory in nonsevere adult subjects with a history of anaphylaxis reactions of grade ≤3. The first 2 cohorts of severe adults (grade 4 or 5 anaphylaxis subjects) were to be treated using both dose regimens at a dose 2 levels below the maximum tolerated dose in nonsevere adults (ie, with 100 µg if 500 µg was the maximum tolerated dose in nonsevere adults). If this 100-µg dose was well tolerated as judged by the DSMB, then 250 µg was to be tested in 2 more cohorts of severe adults. If 250 µg was well tolerated in this population, 2 more cohorts of severe adults were to be treated with 500 µg. At each dose, the 2 dosing regimens were to be evaluated (ie, 24 or 48 hours of patch application).

Number of Patients (planned and analyzed): A total of 110 subjects were planned to be enrolled, (80 nonsevere subjects plus 30 severe subjects). Seventy nonsevere subjects and 30 severe subjects were enrolled and completed the study. The last 2 child cohorts, which were to be treated at the highest dose of 500 µg (10 nonsevere child subjects), did not enroll based on the recommendation of the DSMB.

The safety population included all randomized subjects who received any amount of study medication. The safety population was used as the primary analysis population for the study endpoints.

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Diagnosis and Main Criteria for Inclusion: Male or female subjects aged 6 to 50 years (adults, adolescents, and children) with a known allergy to peanut and a peanut-specific immunoglobulin E (IgE) measured by ImmunoCAP® >0.7 kU/L.

Investigational Product: DBV712 Peanut Allergy Vaccine (or DBV712 or Viaskin® Peanut) Viaskin disk (or Viaskin patch)

Dose: 20 µg, 100 µg, 250 µg, and 500 µg of peanut proteins per patch for a period of 2 weeks.

Regimen: 1 application of DBV712 Viaskin disk (or Viaskin patch) every 24 hours or 1 application of DBV712 Viaskin disk (or Viaskin patch) every 48 hours.

Mode of Administration: Epicutaneous

Reference Product: Placebo

Regimen: 1 application of placebo disk (placebo patch) every 24 hours or 1 application of placebo disk (or placebo patch) every 48 hours.

Mode of Administration: Epicutaneous
The terms disk and patch are used interchangeably in this report to describe the product delivery system.

Batch Number: The lot numbers used in this study (encompassing both active and placebo) were CCI [redacted]

Criteria for Evaluation:
Safety and Tolerability of Repeated Application: Safety and tolerability of repeated applications of DBV712 were assessed by description and tabulation of all adverse events (AEs), treatment-emergent AEs (TEAEs and L-TEAEs), and serious AEs (SAEs). Skin reactions at site of the Viaskin patch (L-TEAEs) were regularly examined and graded by investigators. Physical examinations, atopic dermatitis scoring, vital signs (heart rate, blood pressure, respiratory rate, and temperature), 12-lead electrocardiograms (ECGs), spirometry, peak expiratory flow (PEF) measures, urinalysis, skin prick tests (SPTs), and laboratory tests were also collected.

Safety of DBV712 Treatment: Safety of DBV712 treatment was assessed by the proportion of subjects who experienced systemic reactions related to DBV712. Analysis was also performed on the proportion of subjects requiring treatment for systemic reactions related to DBV712 treatment.

Overall Compliance: Overall compliance to study treatment was assessed by study medication accountability information, which was recorded on the Viaskin accountability case report form (CRF).

Statistical Methods:
Safety and Tolerability of Repeated Application: Adverse events were collected on the CRF and coded via system organ class (SOC) and preferred term (PT) using *Medical Dictionary for Regulatory Activities* (MedDRA) version 13.0. Treatment-emergent AEs were summarized by cohort, overall (pooled placebo and pooled active), and by dose groups. For all TEAE and SAE tables based on the pooled data, the chi-square test or Fisher exact *P* value test comparing the proportion of

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TEAEs between the 2 treatment groups (ie, combined subjects for all dose levels and regimen type for each treatment group) was provided at the SOC level. Physical examination findings were listed by visit, time point, cohort, and overall (pooled placebo and pooled active treatments). Atopic dermatitis scoring and assessment of Viaskin disk site examination were collected at all visits and summarized descriptively. Spirometry was summarized descriptively. Vital signs and ECGs were descriptively summarized by visit, time point, cohort, and overall. All laboratory parameters were listed and sorted by cohort, subject, collection date, and laboratory test.

Safety of DBV712 Treatment and Overall Compliance: Secondary endpoints were summarized descriptively by cohort and by pooled data. The summaries include frequencies and corresponding percentages. The chi-square test was used, when appropriate, to compare the proportion of subjects between the 2 treatment groups (ie, the combined subjects for all dose levels and regimen type for each treatment group).

Results:

The following is a description of cohorts and subjects that were dosed during the study:

- Cohorts 1 through 8 correspond to nonsevere adults;
- Cohorts 9 through 12 correspond to nonsevere adolescents;
- Cohorts 19 and 20 correspond to nonsevere children; and
- Cohorts 13 through 18 correspond to severe adults.

Demographics:

A total of 100 subjects were randomized and treated: 70 nonsevere and 30 severe subjects, including 70 adults, 20 adolescents, and 10 children. Subjects in Cohorts 1, 5, 6, 7, 8, 9, 10, 11, 14, 15, 17 and 20 were predominantly male (≥50%). Subjects in Cohorts 2, 3, 4, 12, 13, 16, 18 and 19 were predominantly female (≥50%).

Overall, subjects who received DBV712 were predominantly male (62.5%), Caucasian (77.5%), and non-Hispanic (95.0%). The mean age of subjects receiving DBV712 was 24.7 years. The overall mean peanut-specific IgE value was 22.73 kU/L and the overall median peanut-specific IgE value was 9.89 kU/L.

Subjects who received placebo were Caucasian (80.0%) and non-Hispanic (90.0%) and evenly divided between male (50.0%) and female (50.0%). The mean age of subjects receiving placebo was 22.2 years. The overall mean peanut-specific IgE value was 36.46 kU/L and the overall median peanut-specific IgE value was 21.75 kU/L.

On average, subjects in this study were predominantly young adult non-Hispanic Caucasians, with a mean peanut-specific IgE value of 25.47kU/L and a median peanut-specific IgE value of 11.20 kU/L. Subjects were polyallergic and 63/100 subjects had concomitant asthma, 45/100 subjects had allergic rhinitis, 13/100 subjects had atopic dermatitis, and 24/100 subjects had eczema. These subjects were highly representative of the peanut-allergic populations.

Safety and Tolerability:

Overall, DBV712 was safe and well tolerated, with no statistically significant differences in overall TEAEs in subjects who received DBV712 versus subjects who received placebo, even though DBV712 triggered more local reactions (L-TEAEs) than placebo in peanut-allergic subjects. There were no deaths, no SAEs, and only 4/100 subjects discontinued during the course of this study, 3 subjects who discontinued due to AEs, and 1 subject who discontinued due to consent withdrawal.

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Among the 3 subjects who discontinued due to AEs, one subject on active treatment in Cohort 19 (child, 250 µg, 1 Viaskin patch/48 hours) was discontinued by the investigator due to TEAEs of moderate vomiting, mild eye pruritus, mild nasal congestion, and mild throat irritation; 1 subject on active treatment in Cohort 13 (severe adult, 100 µg, 1 Viaskin patch/48 hours) was discontinued due to L-TEAE reported by the investigator to be a moderate anaphylactic reaction (local severe pruritus, erythema, edema, urticaria), definitely related to the study treatment. One additional subject on placebo treatment in Cohort 6 (adults, 250-µg placebo, 1 Viaskin patch/24 hours) was discontinued because of protocol noncompliance following a TEAE of moderate anaphylactic reaction, which was considered by the investigator to be definitely related to the study treatment.

Incidences of all TEAEs (assessed either by investigators or by subjects in the diary cards): In each of the cohorts, at least 1 subject experienced a TEAE. The most commonly reported TEAEs were L-TEAEs in the SOC of general disorders and administration site conditions (mostly application site erythema, application site pruritus, application site edema and application site urticaria, all expected L-TEAEs which were prespecified on the diary cards for subject's easy reporting). In most cohorts, 80% or more of the subjects (4/5) experienced an L-TEAE in this SOC.

When comparing DBV712 treatment regimens, ≥87.5% of subjects on both the 1 Viaskin patch/24-hour regimen and the 1 Viaskin patch/48-hour regimen experienced a TEAE. Again, the majority of the events in both regimens were in the SOC of general disorders and administration site conditions. Within that SOC, 50% or more of subjects in all dose groups experienced application site pruritus and application site erythema. For each application site erythema, pruritus, edema or urticaria, more grade 3 L-TEAEs were reported in the 1 Viaskin patch/48-hour regimen than in the 1 Viaskin patch/24-hour regimen. The 100-µg dose group and the 500-µg dose group (1 Viaskin patch/24-hour regimen) experienced a TEAE in the SOC of nervous system disorders, with 2 subjects reporting migraine and 1 subject reporting headache, respectively. All dose groups on the 1 Viaskin patch/48-hour regimen also experienced TEAEs in the SOC of nervous system disorders, with 1 or more subjects in each dose group reporting headache and 1 subject in the 250-µg dose group reported paraesthesia mucosal. Taken together, the results at the level of TEAEs triggered in relation to the regimen of administration of DBV712 suggest that there might be a trend for a slightly better safety profile in the 1 Viaskin patch/24-hour regimen. For the pooled cohorts, DBV712 triggered more local reactions (SOC in the general disorders and administration site conditions) than placebo in peanut-allergic subjects, although there was no statistical difference.

Nonsevere Subjects versus Severe Subjects: The number of subjects with ≥1 TEAE was similar between nonsevere DBV712 subjects (52 of 56 subjects [92.9%]) and severe DBV712 subjects (23 of 24 subjects [95.8%]). There was no statistically significant difference in overall TEAEs (including L-TEAE) in nonsevere DBV712-treated subjects versus severe DBV712-treated subjects, based on Fisher's exact test.

Maximum severity of TEAEs (excluding L-TEAEs reported in the diary cards): For all dose groups, cohorts, and regimens, the majority of TEAEs assessed by investigators (i.e., excluding the application site L-TEAEs directly reported by the subjects in diary cards) were mild in severity and transient. Moderate TEAEs were reported in 7 of 20 cohorts. No severe TEAEs were reported.

Pooled Treatments versus Pooled Placebo (overall): For subjects who received DBV712, 42/80 subjects reported at least 1 TEAE; 33/80 subjects (41.3%) had events of only mild severity and 9/80 subjects (11.3%) had at least 1 event of moderate severity. There were no severe AEs. For subjects who received placebo, 9/20 subjects reported at least 1 TEAE; 6/20 (30.0%) had AEs of only

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mild severity and 3/20 (15.0%) had at least 1 AE of moderate severity. Of note, of the100 subjects treated with any of the Viaskin patch (active or placebo), there were no TEAEs reported for 49 subjects by the investigators. More specifically, this applied to 38/80 of subjects treated with DBV712 (47.5%) and 11/20 subjects treated with placebo (55%).

Nonsevere Subjects versus Severe Subjects (overall): The proportions of subjects with at least 1 TEAE were similar in the nonsevere DBV712 subjects (29 of 56 subjects) compared to the severe DBV712 subjects (13 of 24 subjects). For subjects who received DBV712 in the nonsevere group, 29/56 subjects reported at least 1 TEAE; 24/56 subjects (42.9%) had events of only mild severity and 5/56 subjects (8.9%) had at least 1 event of moderate severity. For subjects who received DBV712 in the severe group, 13/24 subjects reported at least 1 TEAE; 9/24 subjects (37.5%) had events of only mild severity and 4/24 subjects (16.7%) had at least 1 event of moderate severity. No severe TEAEs were reported by subjects in either treatment group.

For subjects who received placebo in the nonsevere group, 6/14 subjects reported at least 1 TEAE; 4/14 subjects (28.6%) had events of only mild severity and 2/14 subjects (14.3%) had at least 1 event of moderate severity. For subjects who received placebo in the severe group, 3/6 subjects reported at least 1 TEAE; 2/6 subjects (33.3%) had events of only mild severity and 1/6 subjects (16.7%) had at least 1 event of moderate severity.

Overall, there was no difference in the proportion of subjects with a TEAE in placebo-treated subjects versus DBV712-treated subjects and no difference between nonsevere and severe subjects in the incidences and severity of TEAEs reported.

Maximum severity reported by subjects for the prespecified L-TEAEs reported in the diary cards: All dose groups or cohorts reported at least 1 local or application site L-TEAE (eg, application site pruritus, application site erythema, application site edema, or application site urticaria) in the diary cards. Nine subjects in 7 cohorts (Cohorts 1, 11, 13, 15, 17, 19, and 20) reported severe L-TEAEs, generally pruritus. These severe L-TEAEs were distributed across 4 nonsevere cohorts and 3 severe cohorts. Of note, only 1 severe adult subject discontinued from the study because of severe L-AEs. Subjects could remove the patch in case of severe L-TEAEs (especially in case of severe pruritus) to allow the severity of the L-TEAE (pruritus) to subside within minutes. They were able to repeat applications at their regimen and remove the patch early as soon as severe pruritus was felt. This process was reiterated until no further severe symptom was reported in which case the patch was then left on for the expected whole duration as per the regimen. All severe L-TEAEs were reported in subjects who received the active Viaskin DBV712 patch. No subjects in any cohort who received placebo reported a severe L-TEAE.

At least 1 subject per cohort who received the active treatment DBV712 except in Cohort 2 (adults, 20-µg dose, 1 Viaskin patch/24 hours) and Cohort 17 (severe adults, 500-µg dose, 1 Viaskin patch/48 hours) reported at least 1 L-TEAE of moderate severity.

Across cohorts, 2 placebo-treated subjects experienced a moderate L-TEAE. In Cohort 2 (adults, 20 µg, 1 Viaskin patch/24 hours) 1 subject (100.0%) reported moderate application site urticaria. In Cohort 19 (children, 250 µg, 1 Viaskin patch/48 hours) 1 subject (100.0%) reported moderate application site pruritus, and moderate application site urticaria.

At least 1 active-treatment subject from each of the 20 treatment cohorts reported at least 1 mild application site or L-TEAE. Placebo-treated subjects from 12/20 treatment cohorts experienced a mild L-TEAE.

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When comparing regimens, it was shown that in both regimens, 3 or more subjects in every dose group reported L-TEAEs in the diary cards. The only dose group in the 1 Viaskin patch/24-hour regimen with a severe L-TEAE was the 250-µg dose group, while the 4 dose groups (20-µg, 100-µg, 250-µg, and 500-µg) in the 1 Viaskin patch/48-hour regimen each reported severe L-TEAEs. This finding suggests a better safety profile for the 1 Viaskin patch/24-hour regimen.

In the DBV712-treated cohorts, 18/40 subjects in the 1 Viaskin patch/24-hour regimen reported at least 1 L-TEAE of moderate severity. In the 1 Viaskin patch/48-hour regimen, 14/40 subjects reported at least 1 L-TEAE of moderate severity. At least 1 subject from each treated group reported 1 moderate L-TEAE. Similarly, 2 placebo-treated subjects reported at least 1 moderate L-TEAE.

In the DBV712-treated cohorts, 14/40 subjects treated with 1 Viaskin patch/24-hour regimen reported only L-TEAE of mild severity. In the 1 Viaskin patch/48-hour regimen, 14/40 subjects reported only L-TEAE of mild severity. Similarly, 4/10 placebo subjects in the 1 Viaskin patch/24-hour regimen and 6/10 placebo subjects in the 1 Viaskin patch/48-hour regimen reported only mild L-TEAE.

Pooled Treatments versus Pooled Placebo (overall): For subjects who received the Viaskin DBV712 patch, 67/80 subjects reported at least 1 L-TEAE in the diary cards. The majority of these subjects, 32/80 (40.0%) reported L-TEAEs of moderate severity; 26/80 (32.5%) of the subjects reported only mild TEAEs and 9/80 (11.3%) reported at least 1 L-TEAE of severe severity. For subjects who received the placebo patch, 12/20 subjects reported at least 1 TEAE in the diary cards. The majority of the subjects 10/20 (50.0%) reported only mild L-TEAEs and 2/20 (10.0%) reported at least 1 moderate L-TEAE. No severe TEAEs were reported by subjects who received the placebo patch.

Local TEAEs like pruritus, erythema, edema or rash are expected reactions at site of patch application during EPIT with DBV712.

Nonsevere versus Severe subjects (overall): For subjects who received DBV712 in the nonsevere group, the majority of these subjects reported L-TEAEs of maximum moderate severity; 45/56 subjects (80.4%) reported at least 1 L-TEAE; 15/56 subjects (26.8%) had only events of mild severity, 24/56 subjects (42.9%) had events of maximum moderate severity, and 6/56 subjects (10.7%) had severe L-TEAEs. For subjects who received DBV712 in the severe group, 22/24 subjects (91.7%) reported at least 1 L-TEAE; 11/24 subjects (45.8%) had only events of mild severity, 8/24 subjects (33.3%) had events of moderate severity, and 3/24 subjects (12.5%) had severe L-TEAEs. For subjects who received placebo in the nonsevere group, 9/14 subjects reported at least 1 L-TEAE; 7/14 subjects (50.0%) had only events of mild severity, 2/14 subjects (14.3%) had events of maximum moderate severity, and no subjects had a severe L-TEAE. For subjects who received placebo in the severe group, 3/6 subjects reported at least 1 L-TEAE; 3/6 subjects (50.0%) had only events of mild severity and no moderate or severe L-TEAEs were reported. There seemed to be a higher proportion of subjects reporting L-TEAEs in the DBV712 severe group; however, there did not seem to be a higher severity in the local reactions in the severe groups versus the nonsevere groups.

Viaskin patch site examination by investigators: In addition to subjects reporting L-TEAEs during the course of the study on diary cards, skin reactions at sites of patch application were examined by the investigators at each study visit and assessed. Local TEAEs at the site of the Viaskin patch application, as assessed by the investigators, were mostly grade 0 or 1 (no skin reaction or erythema with or without infiltration) in DBV712-treated subjects and placebo-treated subjects. For some subjects receiving the DBV712 Viaskin patches, local skin reactions were graded 2 or 3 (erythema,

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infiltration with papules). In parallel, only 2 placebo-treated subjects reported grade 2 local skin reactions. This showed that L-TEAEs were more frequent and more intense in DBV712-treated subjects compared to placebo-treated subjects. There were no grade 4 local skin reactions (erythema with vesicles), a grade which could have led to a study stop pending an expedited safety review.

Nonsevere Subjects versus Severe Subjects (overall): For subjects in both the nonsevere and severe DBV712 and nonsevere and severe placebo treatment groups, the majority of L-TEAEs at all visits and all time points were grade 0 or 1. Nevertheless, grade 2 or 3 L-TEAEs were described in many more nonsevere and severe DBV712-treated subjects than in nonsevere and severe placebo subjects. From the investigators' assessment, the peanut-allergy severity status of subjects did not impact the reactions at the site of the Viaskin disk application with DBV712 treatment. The application-site reactions or L-TEAEs were similar, the majority of which were grade 0 or 1, with some grade 2 or 3 L-TEAEs in both groups with no discernible trends.

Maximum duration of TEAEs (excluding L-TEAEs reported in the diary cards): For all dose groups, the majority of TEAEs were 1 to 7 days in duration. Treatment-emergent AEs of 8 to 14 days in duration were reported in 6 of the 20 cohorts. Treatment-emergent AEs of 15 to 21 days in duration were reported in 1 of the 20 cohorts. Treatment-emergent AEs lasting more than 21 days were reported in 3 of the 20 cohorts.

Regimen Comparison: For both regimens receiving DBV712 or placebo, the majority of TEAEs lasted for 1 to 7 days.

Pooled Treatments versus Pooled Placebo (overall): For subjects who received DBV712, 42/80 subjects reported at least 1 TEAE, and the majority (34/80 [42.5%]) of these subjects reported events that lasted 1 to 7 days. For subjects who received placebo, 9/20 subjects reported at least 1 TEAE, and the majority (7/20 [35.0%]) of these subjects reported events that lasted 1 to 7 days.

Treatment-emergent AEs lasting for a duration of 8 to 14 days were reported by 5 of 80 subjects (6.3%) who received DBV712 and by 1 of 20 subjects (5.0%) who received placebo. Among the subjects who received DBV712, the TEAEs reported with a duration of 8 to 14 days were as follows: cough, mouth ulceration, nasopharyngitis (2 cases), viral upper respiratory tract infection, and hematuria. For the subjects who received placebo, skin infection was the TEAE with a duration of 8 to 14 days.

Treatment-emergent AEs lasting for a duration of 15 to 21 days were reported by 1 of 80 subjects (1.3%) who received DBV712 (application site pruritus).

Treatment-emergent AEs lasting for more than 21 days were reported by 2 of 80 subjects (2.5%) who received DBV712 and by 1 of 20 subjects (5.0%) who received placebo. Among the subjects who received DBV712, reported TEAEs lasting more than 21 days were as follows: eczema and rash. For the subjects who received placebo, the TEAEs lasting more than 21 days were arthritis infective and joint sprain.

Overall, the majority of TEAEs lasted between 1 to 7 days. There did not seem to be any difference in maximum duration of TEAEs in the different dosage groups of DBV712, or according to the 2 regimens of application.

Nonsevere versus Severe Subjects (overall): Overall, the majority of TEAEs lasted between 1 to 7 days in both groups of severity: for 23/56 nonsevere subjects (41.1%) versus 11/24 severe subjects (45.8%) receiving DBV712. The remaining TEAEs subsided progressively over the treatment period.

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Only 2 TEAEs were still ongoing in the nonsevere groups beyond the 21 days of the study.

Maximum duration of L-TEAEs as reported by subjects in the diary cards: In all dose groups, L-TEAEs lasting 1 to 7 days were reported in all 20 cohorts with a similar incidence in subjects receiving DBV7 12 (29/80 [36.3%]) as compared to those receiving placebo (9/20 [45%]). Local-TEAEs lasting 8 to 14 days were reported in 19 of the 20 cohorts. There was a higher incidence of TEAEs lasting 8-14 days in subjects receiving DBV712 (23/80 [28.8%]) than in those receiving placebo (3/20 [15.0%]). Local TEAEs lasting15 to 21 days were reported in 9 of the 20 cohorts. Only subjects treated with DBV712 reported L-TEAEs lasting 15 to 21 days on their diary pages (site pruritus (11/80 subjects [13.8%]), site erythema (6/80 subjects [7.5%]), site urticaria (5/80 subjects [6.3%]) and/or site edema (3/80 subjects [3.8%]). The most common L-TEAE reported for this duration was pruritus. Of note, at Days 15-21, subjects were not under treatment anymore. Local TEAEs lasting more than 21 days were reported in 2 of the 20 cohorts as follows: 1 subject in Cohort 12 (adolescents, 500 µg, 1 Viaskin patch/24 hours) and 1 subject in Cohort 20 (children, 250 µg, 1 Viaskin patch/24 hours) both reported site erythema. Both subjects were previously receiving DBV712.

Regimen Comparison for 1 Viaskin patch/24 hours versus 1 Viaskin patch/48 hours: For both regimens receiving DBV712 or placebo, the majority of L-TEAEs lasted for 1 to 7 days. For subjects in the 1 Viaskin patch/24-hour regimen and the 1 Viaskin patch/48-hour regimen receiving placebo, no TEAEs lasting more than 14 days were reported.

Pooled Treatments versus Pooled Placebo (overall): For subjects who received DBV712, 67/80 subjects reported at least 1 L-TEAE, and the majority (29/67 [43.3%]) of these subjects reported events which lasted 1 to 7 days. For subjects who received placebo, 12/20 subjects reported at least 1 L-TEAE, and the majority (9/12 [75.0%]) of these subjects reported events which lasted 1 to 7 days. Local-TEAEs with a duration of 8 to 14 days were reported by 23/80 subjects (28.8%) who received DBV712 and 3/20 subjects (15.0%) who received placebo. Local TEAEs with a duration of 15 to 21 days were reported by 13/80 subjects (16.3%) who received DBV712 and no L-TEAEs were reported for subjects who received placebo. Local TEAEs lasting for more than 21 days were reported by 2/80 subjects (2.5%) who received DBV712 and by no subjects who received placebo.

Overall, for the subjects who reported L-TEAE on their diary cards, the duration of these L-TEAEs lasted between 1 to 14 days (which corresponded to the duration of treatment) for 52/67 under DBV712 and 12/12 under placebo. Of note, most L-TEAEs lasted only 1 to 7 days (38/79 subjects). Local TEAEs lasting from 8-14 days were in majority reported for subjects who received DBV712: pruritus and erythema were the 2 L-TEAEs lasting longer. L-TEAEs resolved rapidly when the treatment was discontinued as shown by the fact that almost all L-TEAEs still persisting at time of treatment discontinuation have subsided within a week after treatment.

There did not seem to be any difference in duration of L-TEAEs between the different dosage groups of DBV712, or between the 2 regimens of application. However, there was a difference in the duration of the L-TEAEs between the subjects receiving DBV712 and those receiving placebo beyond 15 days. Duration of the L-TEAEs, especially pruritus and erythema, seemed to persist for another week before disappearing for subjects receiving DBV712 as compared to those receiving placebo.

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Nonsevere Subjects versus Severe Subjects (overall): Overall, the majority of L-TEAEs reported by subjects in both groups lasted up to 14 days when treated with DBV712, although a few resolved between Days 8 and 14. These L-TEAEs resolved in both groups of severity after discontinuation of treatment (from Days 15 to 21), with only 2 remaining L-TEAEs beyond 21 days in the nonsevere groups. For the 2 groups of peanut-allergy severity receiving placebo, L-TEAEs were reported by 42.9% of nonsevere and 50.0% of severe subjects with a duration of 1 to 7 days. All TEAEs resolved within 7 days in the severe group, while L-TEAEs resolved by Day 14 for 21.4% of nonsevere subjects. There seemed to be no correlation between the severity of peanut allergy and the duration of the L-TEAEs to DBV712 or placebo.

Potentially drug-related TEAEs (excluding L-TEAEs reported in the diary cards): TEAEs that were potentially drug-related were reported for subjects in 11 of the 20 cohorts and for a total of 19/100 subjects who were randomized and treated (15/70 nonsevere and 4/30 severe).

Regimen Comparison: Both regimens reported TEAEs that were potentially drug-related. Overall, 7 subjects in the 1 Viaskin patch/24-hour regimen reported TEAEs that were potentially drug-related versus 12 subjects in the 1 Viaskin patch/48-hour regimen.

Pooled Treatments versus Pooled Placebo (overall): Subjects in both the pooled treatments (16/80 [20.0%]) and the pooled placebo (3/20 [15.0%]) groups presented at least 1 TEAE considered potentially study drug-related. For subjects who received DBV712, the majority of potentially drug-related TEAEs were in the SOCs of skin and subcutaneous tissue disorders (7.5%), respiratory, thoracic and mediastinal disorders (6.3%), eye disorders (6.3%) and gastrointestinal disorders (5.0%). For subjects who received placebo, the majority of the potentially drug-related TEAEs were in the SOCs of general disorders and administration site conditions (5.0%), skin and subcutaneous tissue disorders (5.0%), and immune system disorders (5.0%).

There was no overall difference in the pooled treated groups versus the placebo groups for the potentially drug-related events.

Nonsevere Subjects versus Severe Subjects (overall): For subjects who received DBV712, 12/56 subjects (21.4%) in the nonsevere group and 4/24 subjects (16.7%) in the severe group, experienced TEAEs that were considered potentially study drug-related. For nonsevere subjects who received DBV712, the majority of potentially drug-related TEAEs were in the SOCs of respiratory, thoracic and mediastinal disorders (8.9%), eye disorders (8.9%), gastrointestinal disorders (7.1%), and skin and subcutaneous tissue disorders (7.1%). In the severe DBV712 group, the majority of potentially drug-related TEAEs were in the SOCs of general disorders and administration site conditions (8.3%), skin and subcutaneous tissue disorders (8.3%), and immune system disorders (8.3%).

For subjects who received placebo, in the nonsevere group, 3/14 subjects (21.4%) experienced TEAEs that were considered potentially study drug-related; the majority of the potentially drug-related TEAEs were in the SOCs of general disorders and administration site conditions (7.1%), skin and subcutaneous tissue disorders (7.1%), and immune system disorders (7.1%). No subjects in the severe group reported a drug-related TEAE.

There was no overall difference in the nonsevere and severe DBV712 groups versus the nonsevere and severe placebo groups for the potentially drug-related events.

Adverse events of special interest: AEs of special interest include local skin reactions of grade 4 as per the EAACI-GA^{2}LEN position paper and any occurrence of anaphylaxis or systemic allergic

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reaction which was directly related to DBV712 treatment or placebo as judged by the investigators.

No grade 4 local skin reactions at the site of application were reported. Hence, AEs of special interest were only limited to systemic allergic reactions related to DBV712 or placebo.

Regimen Comparison for 1 Viaskin patch/24 hours versus 1 Viaskin patch/48 hours: Subjects in both regimens experienced systemic reactions of special interest.

In the 1 Viaskin patch/24-hour regimen, (receiving DBV712), 1 subject (12.5%) in the 100-µg dose group experienced eczema, 3 subjects (18.8%) in the 250-µg dose group experienced reactions which included dyspnea, vomiting, rash, and chest discomfort, and 2 subject (16.7%) in the 500-µg dose group experienced eyelid edema, rhinorrhea, sneezing, lip edema, urticaria, and hypersensitivity.

In the 1 Viaskin patch/48-hour regimen, (receiving DBV712), 2 subjects (25.0%) in the 100-µg dose group experienced pruritus and anaphylactic reaction, 4 subjects (25.0%) in the 250-µg dose group experienced events including eye edema, eye pruritus, increased lacrimation, orbital edema, nasal congestion, throat irritation, vomiting, nausea, atopic dermatitis, pruritus, urticaria, paresthesia mucosal, and pallor, and 1 subject (8.3%) in the 500-µg dose group reported eye edema.

In the 1 Viaskin patch/24-hour regimen, (receiving placebo), 1 subject (25.0%) in the 250-µg dose group, experienced anaphylactic reaction.

In the 1 Viaskin patch/48-hour regimen, (receiving placebo), 1 subject (25.0%) in the 250-µg dose group, experienced urticaria.

Pooled Treatments versus Pooled Placebo (overall): 13 of 80 subjects (16.3%) in the DBV712-treated group and 2 of 20 (10.0%) in the placebo-treated group, reported at least 1 systemic reaction.

There does not seem to be any difference in the frequency of occurrence of the TEAEs of special interest in the DBV712-treated subjects compared to the placebo-treated subjects. Adverse events of special interest were reported with DBV712 in the 100-µg, 250-µg, and 500-µg dose groups only without clear evidence of any dose effect.

Nonsevere Subjects versus Severe Subjects (overall): The following treatment groups reported TEAEs of special interest: 25 TEAEs in the nonsevere DBV712-treated group, 5 TEAEs in the severe DBV712-treated group, 4 TEAEs in the nonsevere placebo group, and no TEAEs in the severe placebo group.

For subjects who received DBV712, in the nonsevere group, 10/56 subjects (17.9%) reported at least 1 systemic reaction: subjects reported gastrointestinal disorders (7.1%), eye disorders (8.9%), respiratory, thoracic and mediastinal disorders (8.9%), and skin and subcutaneous tissue disorders (7.1%). A total of 3/24 (12.5%) severe subjects who received DBV712 reported at least 1 systemic reaction: subjects reported skin and subcutaneous tissue disorders (8.3%) and immune system disorders (8.3%).

For subjects who received placebo, in the nonsevere group, 2/14 (14.3%) reported at least 1 systemic reaction: subjects reported skin and subcutaneous tissue disorders (7.1%) and immune system disorders (7.1%).

There does not seem to be any difference in the frequency of occurrence of TEAEs of special interest in the DBV712-treated subjects compared to the placebo-treated subjects.

Systemic reactions of special interest requiring treatment for all dose groups: Systemic reactions of special interest that required treatment were recorded for 7 cohorts corresponding to 10 subjects. The TEAEs that required treatment occurred in the SOCs of eye disorders, skin and subcutaneous tissue

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disorders, immune system disorders, respiratory, thoracic and mediastinal disorders, gastrointestinal disorders and general disorders and administration site conditions.

Regimen Comparison: 1 Viaskin patch/24 hours versus 1 Viaskin patch/48 hours: Subjects in both regimens experienced systemic events of special interest requiring treatment. In the 1 Viaskin patch/24-hour regimen, 4 subjects receiving DBV712 experienced systemic events of special interest requiring treatment: 1 subject (12.5%) in the 100-µg dose group, 1 subject (6.3%) in the 250-µg dose group, and 2 subjects (16.7%) in the 500-µg dose group. In the 1 Viaskin patch/48-hour regimen, 5 subjects receiving DBV712 experienced systemic events of special interest requiring treatment: 1 subject (12.5%) in the 100-µg dose group, 3 subjects (18.8%) in the 250-µg dose group, and 1 subject (8.3%) in the 500-µg dose group. Only 1 subject receiving placebo in the 1 Viaskin patch/48-hour regimen had TEAEs of special interest requiring treatment.

The highest percentages of subjects with systemic reactions requiring treatment were seen in subjects receiving 500 µg of DBV712 (1 Viaskin patch/24-hour regimen) and in subjects receiving 250 µg of DBV712 (1 Viaskin patch/48-hour regimen).

Pooled Treatments versus Pooled Placebo (overall): Nine subjects in the DBV712-treated group received treatment for their TEAE of special interest versus only 1 subject in the placebo-treated group. In total, of 17 treated TEAEs of special interest, 16 were reported by the subjects in the DBV712-treated group.

Clinical laboratory evaluations: There were no significant changes in hematology, serum chemistry, or urinalysis results over the course of the study for any individual cohorts, regimens, pooled treatment groups, or groups of severity to peanut allergy. In addition, neither DBV712 nor placebo treatment was associated with significant changes from Baseline to Visit 6 in peanut-specific IgE.

Vital signs and physical findings: There were no clinically significant changes in vital signs parameters (pulse, systolic blood pressure, diastolic blood pressure, and temperature) from Screening to the end of treatment for any individual cohorts, regimens, pooled treatment groups, or groups of severity to peanut allergy. The Atopic Dermatitis (AD) status of subjects treated with DBV712 appeared unchanged over the course of the study. Skin prick test to peanut also demonstrated no significant differences between cohorts, regimens, pooled treatment groups, or groups of severity to peanut allergy. Mean and median change from Baseline for PEF was ≤20% across most of the cohorts and regimens; there were also no consistent differences in FEV_1 values from Screening to Visit 6 across cohorts and regimens, indicating that DBV712 did not impact the pulmonary function of the subjects, including subjects with a history of asthma. Finally, there were no clinically significant changes from Baseline in any ECG parameters over the course of the study for any individual cohorts, regimens, or pooled treatment groups.

Concomitant medications: In every cohort, at least 1 subject reported the use of a concomitant medication. The most commonly reported concomitant medications of interest included topical hydrocortisone, inhaled salbutamol, oral diphenhydramine, and oral diphenhydramine HCl. The concomitant use of topical hydrocortisone was reported by subjects in 16 of the 20 cohorts, concomitant use of inhaled salbutamol was reported by subjects in 18 of the 20 cohorts, concomitant use of oral diphenhydramine was reported by subjects in 10 of the 20 cohorts, and concomitant use of oral diphenhydramine HCl was reported by subjects in 14 of the 20 cohorts.

The use of concomitant medications was independent of the regimen of administration.

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Pooled Treatments versus Pooled Placebo: For subjects who received DBV712, 76/80 subjects (95.0%) took at least 1 concomitant medication during the study or follow-up period. The most commonly reported concomitant medications (≥10%) of interest included topical hydrocortisone, inhaled salbutamol, oral diphenhydramine HCl, oral diphenhydramine, oral loratadine, and oral cetirizine. For subjects who received placebo, 100.0% (20/20 subjects) took at least 1 concomitant medication during the study or follow-up period. The most commonly reported concomitant medications (≥10%) included topical hydrocortisone, inhaled salbutamol, oral diphenhydramine HCl, oral diphenhydramine, and oral loratadine.

Nonsevere Subjects versus Severe Subjects: Subjects treated with DBV712 who received at least 1 concomitant medication were 52/56 (92.9%) in the nonsevere group and 24/24 (100.0%) in the severe group; for subjects who received placebo, 14/14 (100.0%) in the nonsevere group and 6/6 (100.0%) in the severe group received at least 1 concomitant medication. Hence, only a few subjects in the nonsevere group did not receive any concomitant medication.

Because most of these subjects had several other allergies, antihistamines were prescribed prior to enrollment in the study and were taken as needed during the treatment period. The most commonly reported concomitant medications were topical hydrocortisone, inhaled salbutamol, oral diphenhydramine HCl, oral diphenhydramine, oral loratadine, and oral cetirizine.

Overall Compliance:
Most cohorts reported a 15-day duration of exposure as per the protocol. The mean cumulative dose of peanut proteins received ranged from 144-µg to 7200-µg across all groups. The mean compliance across all groups was similar and ranged from 97.1% to 102.9% (Note that compliance >100% could be achieved if a subject used more patches than planned for a specific duration of treatment).

For subjects on the 1 Viaskin patch/24-hour regimen (receiving DBV712), the mean compliance reported for each dose group was at least 98.2%.

For subjects on the 1 Viaskin patch/48-hour regimen (receiving DBV712), the mean compliance reported for each dose group was at least 98.2%.

Overall compliance to study medication between the 2 regimens of application was similar.

Pooled Treatments versus Pooled Placebo (overall): The mean duration of exposure and compliance were similar between the pooled treatments and the pooled placebo.

Nonsevere Subjects versus Severe Subjects: The mean duration of exposure was similar between nonsevere DBV712 subjects (14.6 days) and severe DBV712 subjects (14.5 days). Duration of treatment for the severe placebo subjects was 15.0 days and 14.4 days for the nonsevere placebo subjects. Mean cumulative dose received in the DBV712 groups was greater for severe subjects (3016.7 µg) than for nonsevere subjects (2749.6 µg). Compliance to study medication was similar between nonsevere subjects and severe subjects in both treatment groups, with a mean compliance rate of 99.74% in nonsevere DBV712 subjects and 101.19% in severe DBV712 subjects and a mean compliance rate of 101.53% in nonsevere placebo subjects and 100.0% in severe subjects.

This showed that globally, the epicutaneous route for peanut exposure using DBV712 (or its related placebo) resulted in good overall adherence and compliance in nonsevere adults, adolescents, and children allergic to peanut, as well as in severe adults when applied every 24 hours or when applied every 48 hours.

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Summary and Conclusions

Discussion and Overall Summary

There were no deaths, no SAEs, and only 4/100 subjects discontinued during the course of this study, 3 subjects who discontinued due to AEs, and 1 subject who discontinued due to consent withdrawal. There was no statistically significant difference in the overall TEAEs among the nonsevere and the severe DBV712-treated subjects versus placebo-treated subjects. However, DBV712 triggered more L-TEAEs than placebo in peanut-allergic subjects, the majority of these L-TEAEs being mild to moderate and lasting longer than the placebo-triggered L-TEAEs. A slight trend for a better safety profile with the 1 Viaskin patch/24-hour regimen was also noted.

Primary Safety Endpoint

As expected, when DBV712 Viaskin patches were applied epicutaneously, the most commonly reported TEAEs were in the SOC of general disorders and administration site conditions, more specifically L-TEAEs (mostly site pruritus, site erythema, site edema or site urticaria) at the site of application of the patches. DBV712 triggered more local reactions than placebo in peanut-allergic subjects. The majority of these L-TEAEs across the cohorts, regimens and pooled groups of subjects treated with DBV712 were mild to moderate in severity as assessed by the subjects, and did not result in treatment discontinuation for 8 of the 9 subjects who graded these L-TEAEs as severe (especially the pruritus). Placebo-treated subjects noticeably reported L-TEAEs of lower severity, most of them being mild, a few moderate and none graded as severe. The severity of L-TEAEs decreased with time during treatment with DBV712 and when DBV712 was discontinued after the 2 weeks of treatment, all L-TEAEs completely resolved within a week but 2 cases of mild erythema. Skin reactions at the site of application of the patches, (L-TEAEs) were not only daily reported by the subjects in their diary but also examined by the investigators at each study visit from Visit 2 (Day 1) through Visit 7 (Day 22). Local skin reactions, as assessed by the investigators, were mostly of grade 0 or 1 (no skin reaction or erythema with or without infiltration) even in the severe cohorts, in DBV712-treated subjects and placebo-treated subjects. For some subjects receiving the DBV712 Viaskin patches, local skin reactions were grade 2 or 3 (erythema, infiltration with papules); grade 3 reactions were reported only 4 times, none being in the severe cohorts. Skin reactions can subside or be resolved even if DBV712 patches are applied repeatedly on the skin of peanut-allergic subjects. There were no grade 4 local skin reactions (erythema with vesicles).

When considering other types of TEAEs (all TEAEs but the L-TEAEs reported by subjects in the diary cards), one-half of the subjects treated with DBV712 had no TEAE; and when they occurred, the TEAEs were mostly mild and transient.

DBV712 did not impact or worsen the pre-existing skin disorders of subjects with eczema and/or atopic dermatitis. Hence, severe or nonsevere peanut-allergic subjects with eczema or atopic dermatitis can be considered for EPIT with DBV712, as long as they present sufficient zones of intact skin for the application of the patch.

DBV712 did not trigger any significant change in PEF or FEV_1 values, or any exacerbation of the asthma in severe or nonsevere peanut-allergic subjects with pre-existing asthma conditions. Hence, severe or nonsevere peanut-allergic subjects with asthma can be considered for EPIT with DBV712.

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There was no significant difference in change from Baseline for either hematology, biochemistry, urinalysis or peanut-specific IgE values in any pooled cohort for subjects who received DBV712 versus subjects who received placebo using either of the 2 dosing regimens.

No significant changes were seen in potentially clinically significant vital signs parameters (pulse, systolic BP, diastolic BP and temperature) from Screening to the end of treatment in severe or nonsevere subjects treated with DBV712.

Physical evaluations, SPTs and ECG were also unaffected in severe or nonsevere subjects treated with DBV712.

Both DBV712 dosing regimens, the 24-hour regimen and the 48-hour regimen, were safe and well tolerated with a slight better profile for the 24-hour regimen.

Consequently, DBV712 applied repeatedly on the skin of severe or nonsevere peanut-allergic subjects was safe and well tolerated. DBV712 can be contemplated for further clinical development for treating peanut allergy.

The MTD for each age group population recommended for forthcoming studies with DBV712 was assessed to be:

- 250 µg for nonsevere children (6 to 11 years);
- 500 µg for nonsevere adolescents (12 to 17 years);
- 500 µg for nonsevere and severe adults (18 years and above).

Secondary Safety Endpoints

There was no statistically significant difference in the proportion of subjects who required treatment for TEAEs of special interest (defined as any occurrence of anaphylaxis or allergic systemic reactions related to study drug, and any local skin reactions of grade 4) in the DBV712-treated subjects versus the placebo-treated subjects based on Fisher's exact test. In the AEs of special interest identified, there were no local grade 4 skin reactions.

Exactly half of the TEAEs of special interest did not require any treatment, and resolved spontaneously, in nonsevere as well as in severe peanut-allergic subjects.

Overall adherence to the study treatment, as measured by compliance, was similar and high (over 96%) in nonsevere or severe subjects who received DBV712 or placebo. Hence, the adherence to the study treatment consisting of applying peanut proteins on the skin using the DBV712 Viaskin patch was good and well accepted by all categories of peanut-allergic subjects, nonsevere or severe.

The epicutaneous route for peanut exposure using DBV712 resulted in a good overall adherence and compliance in all subjects allergic to peanut, when applied every 24 hours or when applied every 48 hours.

Overall Conclusion

The peanut-allergic nonsevere and severe adults, nonsevere adolescents, and nonsevere children randomized in this study presented high peanut-specific IgE levels (mean value of 25.47 kU/L and median value of 11.20 kU/L). They were polyallergic subjects (with other food allergies and/or other

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airborne allergies), 63% of the subjects had asthma, 45% had allergic rhinitis, and regarding pre-existing skin disorders, 13% of subjects had atopic dermatitis, and 24% subjects had eczema.

In these subjects, DBV712 was safe and well tolerated. Both regimens of application, 1 Viaskin patch/24 hours and 1 Viaskin patch/48 hours were safe, with a slightly better safety profile for the 1 Viaskin patch/24 hours dosing regimen.

There was no statistically significant difference in the overall TEAEs among the nonsevere and the severe DBV712-treated subjects versus placebo-treated subjects. However, DBV712 triggered more local reactions than placebo in peanut-allergic subjects. Safety was shown in nonsevere peanut-allergic adults, adolescents and children, as well as in severe peanut-allergic adults.

The maximal doses of DBV712 tolerated in the different subject populations were as follows:

– 250 µg for nonsevere children (6 to 11 years);
– 500 µg for nonsevere adolescents (12 to 17 years);
– 500 µg for nonsevere and severe adults (18 years and above).

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