REDUCTION IN SEVERITY FOLLOWING 12 MONTHS OF EPICUTANEOUS IMMUNOTHERAPY FOR PEANUT ALLERGY

#342

Philippe Bégin,[1] J. Andrew Bird,[2] Jonathan M. Spergel,[3] Dianne E. Campbell,[4,5] Todd D. Green,[4,6] Katharine J. Bee,[4] Romain Lambert,[4] Hugh A. Sampson,[4,7] David M. Fleischer[8]

[1]CHU Sainte-Justine, Montreal, QC, Canada; [2]University of Texas Southwestern Medical Center, Dallas, TX, USA; [3]Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]DBV Technologies, Montrouge, France; [5]The Children's Hospital at Westmead, Sydney, NSW, Australia; [6]UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, USA; [7]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [8]Children's Hospital Colorado, University of Colorado, Aurora, CO, USA

RATIONALE

- Peanut allergy, one of the most common food allergies, can result in severe, potentially life-threatening reactions[1,2]
- A major goal of food allergy immunotherapy is to reduce the likelihood of reactions to accidental allergen ingestion by desensitization, ie, increasing the reactivity threshold or the eliciting dose (ED)[3-5]
- Another important goal of food allergy immunotherapy for both caregivers and patients is the reduction in severity of reactions to accidental ingestion[3,6]
- The 12-month Phase 3 PEPITES clinical trial demonstrated that daily epicutaneous immunotherapy (EPIT) with DBV712 250 µg (approximately 1/1000 of a peanut) was statistically superior to placebo in desensitizing peanut-allergic children aged 4 to 11 years based on double-blind, placebo-controlled food challenges (DBPCFCs) at study entry and Month 12 post-treatment[4,7]
  - Assessment of severity of allergic reactions at DBPCFC was based upon pre-specified PRACTALL symptoms
- As reducing allergic reaction severity has been articulated as a goal for peanut-allergic patients and their caregivers, it is important to understand the potential role of DBV712 250 µg with respect to this outcome

OBJECTIVE

- To compare the severity of allergic symptoms elicited during standardized DBPCFCs to peanut at baseline and Month 12 between DBV712 250 µg and placebo groups by post hoc analysis of the PEPITES trial

METHODS

- PEPITES was a Phase 3, randomized, double-blind, placebo-controlled clinical trial to assess the efficacy and safety of DBV712 250 µg in 356 children aged 4 to 11 years with physician-diagnosed peanut allergy (**Figure 1**)[4]
  - Subjects in PEPITES were randomized 2:1 to receive DBV712 250 µg or placebo daily for 12 months
- In PEPITES, DBPCFCs were conducted according to PRACTALL guidelines at Month 0 (baseline) and at Month 12 post-treatment using a standardized, blinded food matrix[4,8]

Figure 1. PEPITES Study Design

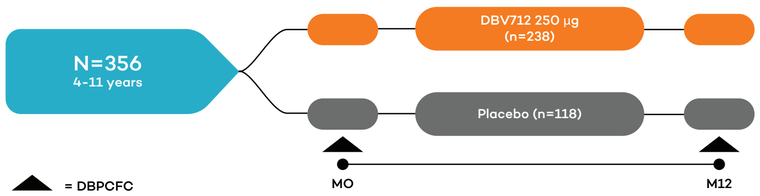

Table 1. Objective Signs/Symptoms Collected During DBPCFC—All Assessable Organ Systems

SKIN	• Erythematous rash (and % of rash area concerned) • Pruritus • Urticaria/angioedema
UPPER RESPIRATORY	• Sneezing/itching • Nasal congestion • Rhinorrhea • Laryngeal
LOWER RESPIRATORY	• Wheezing
GASTROINTESTINAL	• Diarrhea • Vomiting
CARDIOVASCULAR	
EYES	• Conjunctivitis

- DBPCFCs were discontinued when sufficient objective signs or symptoms, shown in **Table 1**, met prespecified stopping criteria and required treatment[4]
  - The peanut protein dose at which objective symptoms resulted in ending the food challenge was considered the subject's ED
- Symptom severity was graded by the investigator as 0–3 at each time point for each PRACTALL symptom (none [0], mild [1], moderate [2], or severe [3]) based on PRACTALL scoring recommendations[6]
- By post hoc analyses, maximum severity of symptoms at baseline and Month 12 was compared between DBV712 250 µg and placebo groups for **all organ systems (AOS)**
  - In order to assess more concerning signs/symptoms with potentially serious clinical consequences, the maximum severity **in 5 significant symptom (5SS) domains** was also compared. These domains were **wheezing, cardiovascular, laryngeal, vomiting, and diarrhea**
- Analyses were performed on the Full Analysis Set (FAS), which included all randomized subjects who underwent at least the peanut challenge of the second DBPCFC at Month 12
- The two-sided exact Cochran-Armitage Trend Test was used to evaluate differences in the distribution of maximum symptom severity between the DBV712 250 µg and placebo treatment groups
- The Fisher Exact Test was used to test between-group differences within a severity grading category

RESULTS

All Organ Systems (AOS)

- The FAS population consisted of 222 subjects in the DBV712 250 µg group and 109 in the placebo group
- At Month 0, the proportions of subjects with mild, moderate, or severe objective signs/symptoms for AOS were similar in each treatment group (P=0.931) (**Table 2**)
- In contrast, there was a significant between-group difference (P<0.001) in the distribution of symptom severity at Month 12 (**Table 2**)
  - Nearly twice as many DBV712 250 µg-treated subjects (31.1%) as placebo-treated subjects (16.5%) had a maximum symptom severity score of "none" or "mild"
  - In addition, the difference in the proportion of subjects with a maximum severity score of "severe" differed significantly between the DBV712 250 µg group (16.2%) and the placebo group (27.5%; P=0.019)

Table 2. Maximum Severity of Objective Signs/Symptoms to Peanut by Treatment Group at Baseline and Month 12 for AOS

MAXIMUM SEVERITY OF OBJECTIVE SYMPTOMS	DBV712 250 µG (n=222)	PLACEBO (n=109)	*P* VALUE
MONTH 0 DBPCFC			
n	222	109	
None	0	0	
Mild	35 (15.8)	12 (11.0)	0.931*
Moderate	101 (45.5)	61 (56.0)	
Severe	86 (38.7)	36 (33.0)	
MONTH 12 DBPCFC			
n	222	109	
None	14 (6.3)	2 (1.8)	
Mild	55 (24.8)	16 (14.7)	<0.001*
Moderate	117 (52.7)	61 (56.0)	
Severe†	36 (16.2)	30 (27.5)	

*Two-sided exact *P* value from Cochran-Armitage Trend Test.
†DBV712 250 µg vs placebo, P=0.019; Fisher Exact Test.

Five Significant Symptom (5SS) Domains

- For the 5SS domains of wheezing, cardiovascular, laryngeal, vomiting, and diarrhea, the proportion of subjects with mild, moderate, or severe signs/symptoms was similar at Month 0 for DBV712 250 µg- and placebo-treated subjects (P=0.946) (**Table 3**)
- Consistent with the prior analysis, there was a statistically significant between-group difference in the distribution of symptom severity at Month 12 post-treatment for the 5SS domains (P=0.016) (**Table 3**)
  - Additionally, 20.7% of subjects in the DBV712 250 µg group had severity scores of "none" compared with 11.0% in the placebo group (P=0.031), nearly a two-fold difference

Table 3. Maximum Severity of Clinically Significant Reactions to Peanut by Treatment Group at Baseline and Month 12 for 5SS Domains (Wheezing, Cardiovascular, Laryngeal, Vomiting, and Diarrhea)

MAXIMUM SEVERITY OF OBJECTIVE SYMPTOMS	DBV712 250 µG (n=222)	PLACEBO (n=109)	*P* VALUE
MONTH 0 DBPCFC			
n	222	109	
None	33 (14.9)	12 (11.0)	
Mild	83 (37.4)	48 (44.0)	0.946*
Moderate	79 (35.6)	38 (34.9)	
Severe	27 (12.2)	11 (10.1)	
MONTH 12 DBPCFC			
n	222	109	
None†	46 (20.7)	12 (11.0)	
Mild	103 (46.4)	50 (45.9)	0.016*
Moderate	63 (28.4)	39 (35.8)	
Severe	10 (4.5)	8 (7.3)	

*Two-sided exact *P* value from Cochran-Armitage Trend Test.
†DBV712 250 µg vs placebo, P=0.031; Fisher Exact Test.

CONCLUSIONS

- This post hoc analysis demonstrated that, in addition to increasing reactivity threshold in 4- to 11-year-old peanut-allergic children, investigational EPIT with DBV712 250 µg may also reduce the severity of allergic reactions
- For all organ systems, as well as 5 significant symptom domains, the distribution of symptom severity scores differed significantly between the DBV712 250 µg and placebo groups at the Month 12 DBPCFC irrespective of ED
- These results suggest that DBV712 250 µg treatment may address dual goals of immunotherapy: decreasing the likelihood of reactions to accidental ingestion of peanut allergy and reducing reaction severity, outcomes of importance to caregivers and patients

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