Symposium
SUNDAY JUNE 7
5:30 to 7:00 pm
Room 116

Epicutaneous Immunotherapy
A Breakthrough Approach in Food Allergy Treatments
Epicutaneous Immunotherapy: Mechanism of Action and Preclinical Data

by Dr. Lucie Mondoulet,
DBV Technologies
In Vivo POC: Sensitized Mice Challenged with Peanut Aerosol

<table>
<thead>
<tr>
<th>SENSITIZATION PPE + CT (6 ig for 6 weeks)</th>
<th>EPICUTANEOUS IMMUNOTHERAPY</th>
<th>HYPERRESPONSIVENESS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3 days of aerosol exposition to peanut powder</td>
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<tr>
<td></td>
<td></td>
<td>Invasive method (resistance-compliance)</td>
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<tr>
<td></td>
<td></td>
<td>Non-invasive method (plethysmography)</td>
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<tr>
<td></td>
<td></td>
<td>BAL fluid content analysis (eosinophil infiltration)</td>
</tr>
</tbody>
</table>

D0  
SENSITIZATION PPE + CT (6 ig for 6 weeks)  
(6 ig for 6 weeks)

D45  
EPIT 100 (n=2 x 10)

D105  
SCIT 100 (n=2 x 10)

Samplings for humoral responses

In Vivo POC: Observed Systemic Efficacy of EPIT®

Humoral Responses

Specific IgE

Specific IgG2a

In Vivo POC: Observed Efficacy in Target Organ

**In Vivo POC:** Sensitized Mice Exposed to peanut regimen Inducing Esophageal Eosinophilia

**SENSITIZATION peanuts + CT**
(6 ig for 6 weeks)

**IMMUNOTHERAPY**

**Naive**

**Sham**

**EPIT 100**

**10-DAY-PEANUT-REGIMEN**
Sampling:
Spleen (cell culture)
Esophagus (histology, mRNA analysis)

In Vivo POC: Observed Efficacy on Challenged Esophageal Tissue


esoinophilic esophagitis in mice : ~100 eosinophils/mm²
Efficacy of EPIT® in Eosinophilic Digestive Disorders

Mondoulet et al, 2013. EAACI meeting

Stomachal samplings blindly analyzed by histology

EPIT® decreases eosinophilic infiltration in stomach

Mondoulet et al, 2013. EAACI meeting
EPIT®: Which players for immunomodulation?
Role of Tregs in EPIT®’s Efficacy

Inhibition of Tregs action by adding anti-CD25 antibody

SENSITIZATION TO PPE

Naive
Sham
EPIT
Anti-CD25 + EPIT

10-DAY-PEANUT-SUSTAINED EXPOSITION

Histology
Splenocytes culture

Dioszeghy et al, 2014. CEA, 44: 867-881
EPIT®'s Efficacy is Mediated by Tregs

Dioszeghy et al, 2014. CEA, 44: 867-881
Protection Against Esophageal Eosinophilia by Adoptively-Transferred EPIT® Tregs

Dioszeghy et al, 2014. CEA, 44: 867-881
Protection of Esophageal Eosinophilia by Isolated EPIT®-Induced Tregs

Adoptive transfer of Tregs generated immediately or 8 weeks after EPIT® prevents from eosinophilic infiltration into esophagus

Dioszeghy et al, 2014. CEA, 44: 867-881
Phenotyping of EPIT®-Induced Tregs

Sampling:
- Spleen cells
- Lymph node cells

Dioszeghy et al, 2014. CEA, 44: 867-881; Dioszeghy et al., submitted
EPIT® induces a unique population of Tregs...

- EPIT® induced Foxp3+ Tregs and not IL-10+ Tregs (Tr1)
- EPIT® induced naive and effector Tregs
- EPIT® increased the CTLA-4 expression on Tregs underlying the cell-contact mediation

Dioszeghy et al, 2014. CEA, 44: 867-881; Dioszeghy et al., submitted
... and a large expression of homing receptors for targeting specific organ

- Lung (CCR4)
- Skin (CLA)
- Gut (CCR9)

High Co-Expression of CCR9 and CLA for EPIT

Dioszeghy et al., submitted
Role of Epigenetic Modifications in the Sustainability of EPIT®-Induced Protection

Mondoulet et al, 2014. AAAAI meeting
EPIT® Induces Sustained Epigenetic Modifications

Mondoulet et al, 2015. EAACI meeting, poster 414 – Monday 10/06 15:45 to 17:00 – PDS 19
From Epigenetics to the Prevention of Allergic Diseases: The Bystander Effect
EPIT® Prevents Further Sensitizations

Mondoulet et al, 2015, JACI, in press
EPIT® Prevents Induction of Th2-mediated Responses to Further Allergens

Mondoulet et al, 2015, JACI, in press
EPIT® Induces Tregs specific to treatment

Mondoulet et al, 2015, JACI, in press
EPIT® Prevents Anaphylaxis to Further Allergens

Milk epicutaneous immunotherapy in sensitized mice prevents further sensitization to peanuts

Mann-Whitney non parametric test
- naive vs Sham, p = 0.0159
- naive vs control+, p = 0.0079
- EPIT vs Sham, p = 0.0079
- EPIT vs control+, p = 0.0079
- naive vs EPIT, p = 0.4127

Mondoulet et al, 2015, JACI, in press
Role of EPIT®-induced Tregs in the protection against anaphylaxis to further allergens

Mondoulet et al, 2015, JACI, in press
EPIT®-induced Tregs are responsible of protection against anaphylaxis to further allergens

Mondoulet et al, 2015, JACI, in press
**Research Conclusions**

**EPIT’s Mechanism of Action in animal models**

- Epicutaneous pathway: *Safety of administration* (no passive passage into bloodstream) and *efficacy* (targeting of LCs)
- Continuous antigen exposure triggers sustained tolerization leading to a potential treatment for allergies: Induction of FoxP3+ *naïve* and *effector Tregs* and deeper *epigenetic modifications*
- Prevention of allergic disease evolution *by allowing an early intervention during the “window of opportunity”*
Epicutaneous Immunotherapy: A Novel Immunotherapy in Food Allergy

by Dr. Christophe Dupont, Necker Hospital, Paris (France)
Viaskin® a novel Immunotherapy in Food Allergy

Pr Christophe DUPONT, MD, PhD,
AP-HP, Necker Hospital, University Paris-Descartes, Paris, France
Conflict of interest

- Co-founder of DBV Technologies
- Chairman, Scientific Advisory Board, DBV Technologies
The ontogeny of EPIT®

• Reference method for immunotherapy: subcutaneous injection of aero-allergens

• Food allergy:
  – subcutaneous injection impossible
The ontogeny of EPIT®

• Further attempts with skin: deposition of aeroallergen on heavily scarifed skin

• Development of Atopy Patch Tests: skin reacts with allergen deposited on intact skin

• Epicutaneous Immunotherapy: therapeutic use of the immune reaction triggered by the allergen deposited on the skin
EPIT® in mouse models

Proof of concept studies:
- Interaction with the skin immune system
  - Multi-organ protection
Targeting of Langerhans cells: antigen processing from the epidermis to the draining lymph nodes

Allergen (OVA-A488)

Epidermis

Dermis

C

D

E

Epidermis

Dermis

LNs

Sensitized
Naive
Possible mechanism of antigen delivery with EPIT®

Fig. 1: Antigen delivery by Viaskin® from epidermis to draining lymph nodes for epicutaneous immunotherapy (EPIT)
DC: dendritic cell; LC: Langerhans cell

Fig. 2: Possible mechanism of action for epicutaneous immunotherapy (EPIT) to treat food allergy.
APC: antigen presenting cell; Baso: Basophil; DC: dendritic cell; Eos: Eosinophils; LC: Langerhans cell; MC: Mast cell; Teff: Effector T cell
Viaskin®: delivery of the allergen onto the intact skin
Viaskin® Patch Architecture

- Dry layer of allergen
- Condensation chamber

Breathable over-adhesive
Adhesive Crown
PET-Titanium Backing
Condensation Chamber
Drug development

• Feasibility: Milk EPIT® (Dupont et al. Jaci 2010)

• Safety and efficacy in children with peanut EPIT®: the Arachild study

• Pharmaceutical development of peanut EPIT®:
  – Phase I study, PEP01
  – Phase IIb study, VIPES
  – Phase IIb prolongation, OLFUS-VIPES
  – Phase III: PEPITES
Clinical use of Viaskin®

- Everyday
- 24 hour application
- 3 years

Viaskin® Peanut patch must be daily applied on the skin for 24 hours on the inter-scapular area of the back of the subjects or the inner side of both upper arms for the adults.
Cow’s milk epicutaneous immunotherapy in children: A pilot trial of safety, acceptability, and impact on allergic reactivity

Volume of Milk tolerated before symptoms appear (ml)

**Active group**

- OFC1 - T0
- OFC2 - 3 months
- OFC3 - 6 months

**Placebo group**

- OFC1 - T0
- OFC2 - 3 months
- OFC3 - 6 months

48h application, 3/week
Nb treated pt=9, Nb placebo pt=7
3-month treatment

Dupont C et al. JACI 2010
## Product in development in Food Allergy

<table>
<thead>
<tr>
<th>PROGRAM</th>
<th>INDICATION</th>
<th>COMMERCIAL RIGHTS</th>
<th>DISCOVERY</th>
<th>PRE-CLINICAL</th>
<th>PHASE I</th>
<th>PHASE II</th>
<th>PHASE III</th>
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</thead>
<tbody>
<tr>
<td>Viaskin Peanut</td>
<td>Peanut Allergy</td>
<td>DBV Worldwide</td>
<td></td>
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<td>FDA Fast Track and Breakthrough Therapy</td>
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<tr>
<td>Viaskin Milk</td>
<td>Cow’s Milk Protein Allergy (CMPA)</td>
<td>DBV Worldwide</td>
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<td>Confirmatory Phase III study</td>
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<tr>
<td>Viaskin Egg</td>
<td>Hen’s Egg</td>
<td>DBV Worldwide</td>
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Viaskin® Peanut Development Plan

Core Development Plan

Phase I

Phase IIb VIPES OLFUS-VIPES

Phase III

Registration

Academic collaborations

Phase Ila Arachild

Proof of Concept

Phase II CoFAR 6

Biomarkers and MoA
Proven safety profile of Viaskin® Peanut – large Phase

Good tolerance in severe and non severe peanut-allergic adults, adolescents and children

- No SAEs: only 2 drop-out due to AE
- Local cutaneous AEs (pruritus, erythema, edema):
  - 90% of patients with Viaskin Peanut vs 50% with placebo
  - Higher in intensity with Viaskin Peanut, well controlled with topical corticosteroids ointments and oral histamines
- Other AEs
  - None in half subjects
  - Mild in intensity and comparable with Viaskin and placebo
- Excellent patient compliance (over 96%)

500 µg: MTD in Adolescents and Adults
250 µg: MTD in Children

Agbotounou W et al. Allergy 2012
ARACHILD Phase II, Multicenter RCT

- **Multicenter randomized (1/1) clinical trial:**
  Viaskin Peanut, 100 μg peanut protein
  Viaskin Placebo (switched at 6 months to Viaskin Peanut without unblinding the study)

- **54 patients:** 35 children (5-11 yrs), 19 adolescents (12-18 yrs), severe peanut allergy

  **At enrolment:** Peanut-specific IgE >5kU/L
  DBPCFC: Cumulative Reactive Dose (CRD) of peanut protein <300 mg
  (Patients with a positive placebo challenge were excluded)

- **Evaluation criteria**
  DBPCFC at 6, 12 and 18 months
  Success: >10-fold increase in initial CRD of peanut protein or CRD >1000 mg (3.3 peanuts)
  Peanut-specific IgE and IgG4 changes
Efficacy: Increasing with treatment duration

All patients, 5-18 years (n=54)  
Children, 5-11 years (n=16)

Viaskin Peanut group follow-up (n=25)

No response in adolescents

Over the study, 4 children ingested >1000 mg of peanut protein (3.3 peanuts) and up to 2.5g

Strong response in children arm with a 67% success rate

Viaskin® Peanut 100 μg
Placebo
VIPES Phase IIb & OLFUS-VIPES: largest study ever in peanut allergy

**Study Design**

**Phase IIb**
- 221 patients, 22 centers, 5 countries*

**Study Population**
- Age: 6 - 55 years old
- Peanut allergic patients (positive peanut-specific IgE and SPT)
- Highly sensitive subjects: DBPFC reactive dose at baseline (M0) ≤ 300 mg peanut protein

**Efficacy Endpoints**
- Primary endpoints: ‘responder rate’ defined as patients reaching ≥ 1000 mg reactive dose or ≥ 10 x initial reactive dose at M12 DBPCFC
- Main secondary endpoints: efficacy in patient populations (CRD, LS Mean, and other measures in children, adolescents, adults), change from baseline in sIgE, sIgG4

*US, Canada, The Netherlands, France, Poland

- **Treatment**
- **Off-Treatment**
- **Food challenges:** Completed, ongoing, Planned
VIPES, Phase IIb – Main results

Confirmed Good Safety Profile & Compliance whatever the age

VIPES met the primary efficacy endpoint

12-Month active EPIT®
- high increase in ability to consume peanut protein
- no serious adverse events related to treatment
Viaskin® Milk Development Plan

Proof of concept

Phase II
Milk

MILES: Phase I/II

Dose Ranging (Safety & Efficacy)

Phase III

Registration

EoE

Phase IIa

J. SPERGEL (The Children’s Hospital of Philadelphia)
MILES Overview

• A Combined **Phase I/II study**

• **24-Month study**: 12-month double-blind treatment (Viaskin Milk or Placebo) followed by 12-month open-label treatment (Viaskin Milk only)

• Study divided in two parts for randomization of subjects:
  - **Part A**: 3 successive cohorts of 6 subjects to initially study the safety of three doses of Viaskin Milk 150 μg, 300 μg, 500 μg versus Placebo (Ratio 2:1)
  - **Part B**: two doses of Viaskin Milk versus Placebo (Ratio 1:1:1)

• **150 subjects randomized** (2-17 years) with IgE-mediated CMA

• **Stratification Children** (2-11 years) / Adolescents (12-17 years)
Conclusion

- Immunotherapy avoiding oral ingestion
- Safest treatment for lifethreatening allergy, very adapted to young children
- Strong proof of concept
- Full pharmaceutical development
- Three clinical trials showing safety and efficacy
- Further steps:
  - Peanut Phase II data will further document EPIT: OLFUS (2 years follow-up), CoFAR
  - Phase III – Peanut study to be initiated in view of registration in North America and Europe
  - Phase I/II – Milk on going
Peanut Epicutaneous Immunotherapy is Effective and Safe to Treat Peanut Allergy: A Multicenter Randomized Controlled Trial (VIPES Study)

by Dr. Hugh Sampson,
Mount Sinai Hospital, New York (USA)
EPicutaneous ImmunoTherapy (EPIT®) is Effective and Safe to Treat Peanut Allergy: A Multicenter Randomized Controlled Trial (RCT) (VIPES Study)

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**Sponsor**  
DBV Technologies
Disclosures
Hugh A Sampson, MD

In relation to this presentation, I declare the following, real or perceived conflicts of interest:

- Allertein Therapeutics, LLC Consultant
- Danone Scientific Advisory Board Consultant
- Regeneron Therapeutics, Inc. Consultant
- Genentech/Novartis Consultant
- Sanofi Scientific Advisory Board Consultant
- UpToDate, Inc. Consultant
- NIAID; NIH Grantee
- Food Allergy Research & Education Grantee
- Herbs Spring, LLC Stockholder

A conflict of interest is any situation in which a speaker or immediate family members have interests, and those may cause a conflict with the current presentation. Conflicts of interest do not preclude the delivery of the talk, but should be explicitly declared. These may include financial interests (e.g. owning stocks of a related company, having received honoraria, consultancy fees), research interests (research support by grants or otherwise), organisational interests and gifts.
VIPES: a Phase IIb - Viaskin® Peanut

Screening

- History of Peanut Allergy
  - 6 to 55 years of age
  - Peanut specific IgE > 0.7 kUa/L
  - Peanut SPT wheal ≥ 8 mm

1 year treatment

- 1st DBPCFC
  - Eliciting dose ≤ 300 mg pp

- 2nd DBPCFC
  - Change in Eliciting dose

- Randomization
  - Placebo
  - 50 µg pp
  - 100 µg pp
  - 250 µg pp

DBPCFC = Double-Blind Placebo-Controlled Food Challenge
pp = peanut protein
### DBPCFC: Efficacy Outcome Scoring

- **Standardized challenge matrix**: chocolate dessert base formula
- **Standardized** semi-logarithmic increase of peanut protein doses every 30 min (as per PRACTALL²)

![Dose Chart](image)

- **Allergic symptoms graded** from a standardized published protocol³ (see below)
- **Challenge stopped in case of objective symptoms** (See below):

#### Objective symptoms

<table>
<thead>
<tr>
<th>I. SKIN</th>
<th>Grade</th>
<th>Subjective symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Erythematous rash: % area involved</td>
<td>0 1 2 3</td>
<td></td>
</tr>
<tr>
<td>B. Pruritus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. Urticaria-Angioedema</td>
<td>0 1 2 3</td>
<td></td>
</tr>
<tr>
<td>D. Rash</td>
<td></td>
<td></td>
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<thead>
<tr>
<th>II. UPPER RESPIRATORY</th>
<th>Grade</th>
<th>Subjective symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Sneezing-Itching</td>
<td>0 1 2 3</td>
<td></td>
</tr>
<tr>
<td>B. Nasal Congestion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. Rhinorrhea</td>
<td>0 1 2 3</td>
<td></td>
</tr>
<tr>
<td>D. Laryngeal</td>
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<thead>
<tr>
<th>III. LOWER RESPIRATORY</th>
<th>Grade</th>
<th>Subjective symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Wheezing</td>
<td>0 1 2 3</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IV. GASTROINTESTINAL</th>
<th>Subjective symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Subjective Complaints</td>
<td>Itchy mouth</td>
</tr>
<tr>
<td></td>
<td>Itchy Throat</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Objective Complaints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
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<tr>
<td>Vomiting</td>
</tr>
</tbody>
</table>

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<tr>
<th>V. CARDIOVASCULAR</th>
<th>Subjective symptoms</th>
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<tbody>
<tr>
<td>Normal heart rate to bradycardia</td>
<td>0 1 2 3</td>
</tr>
</tbody>
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¹Cochrane et al, Allergy 2012; ²Sampson et al, JACI 2012; ³Nowak-Wegrzyn et al, JACI 2009

---

Food challenge to be stopped
Food challenge to be stopped if 2 or more symptoms
### VIPES: Inclusion & Exclusion Criteria

#### Inclusion Criteria
- Age $\geq 6$ years, $< 55$ years
- Peanut-specific IgE $> 0.7$ kU$_A$/L
- Positive peanut SPT wheal $\geq 8$ mm
- Peanut Food Challenge reactive dose $\leq 300$ mg pp

#### Exclusion Criteria
- Medical history of Severe Anaphylaxis to Peanut
- FEV$_1$ $< 80\%$, uncontrolled persistent asthma
- Past or current disease(s) that would affect subject’s participation

#### Study Stratified by Age
- **Children** (6-11 years): 113
- **Adolescents and adults** ($\geq 12$ years): 108
  - Adolescents (12-17 years): 73
  - Adults (18-55 years): 35

#### Breakdown of patients by strata
- Children: 51%
- Adolescents: 33%
- Adults: 16%
Threshold Dose at Enrollment

- **Baseline Median Eliciting Dose**
  - Children (113): 30 mg peanut protein (pp)
  - Adolescents/Adults (108): 100 mg peanut protein

Peanut Eliciting Doses (entry DBPCFC)
Adherence to Treatment

<table>
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<tr>
<th>Statistic</th>
<th>Placebo (N=56)</th>
<th>50 µg (N=53)</th>
<th>100 µg (N=56)</th>
<th>250 µg (N=56)</th>
<th>Total (N=221)</th>
</tr>
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<tbody>
<tr>
<td>Overall compliance</td>
<td>Median (%)</td>
<td>97.0</td>
<td>96.9</td>
<td>97.8</td>
<td>98.7</td>
</tr>
<tr>
<td>Drop-out not related to Viaskin</td>
<td>n (%)</td>
<td>2 (3.6)</td>
<td>2 (3.8)</td>
<td>6 (10.7)</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>Drop-out related to Viaskin</td>
<td>n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.8)</td>
<td>1 (1.8)</td>
</tr>
</tbody>
</table>

- Median compliance rate in all treatment arms ≥ 97%
- Drop out rate = 6.3%, Drop-out for EPIT-related AEs = 0.9%
Safety Profile: Viaskin Peanut

- **20 SAEs, not related to Viaskin Peanut**
  - Related to peanut challenge during DBPCFCs (study procedure): 14 anaphylaxis
  - **Others**: 1 allergic reaction due to fish consumption, 3 accidental consumption of food-containing peanut (moderate anaphylaxis), 1 respiratory distress case, 1 psychiatric case

- **Related to Viaskin Peanut**
  - No use of epinephrine
  - **Most frequent AEs**: Local cutaneous reaction >90% of subjects mainly mild and moderate (50% with a duration < 2 months)
  - 2 withdrawals due to dermatitis

4 DSMB reviews: “No safety concerns”
Primary Efficacy Endpoint

DBPCFC after 12 months of EPIT: % of patients reacting to ≥ 1,000 mg peanut protein OR with ≥ 10-fold increase in their eliciting dose

Main Secondary Efficacy Endpoints

Quantitative changes:
- Eliciting Dose (ED)
- Cumulative Reactive Dose (CRD)
- Peanut-specific IgE and -specific IgG4
Treatment Responders at Month 12
Whole ITT population

*Primary efficacy endpoint met

≥1000 mg at Month 12
Treatment Responders at Month 12
6-11 yrs of age

Efficacy demonstrated with all 3 Viaskin Peanut doses
Change from baseline CRD at Month 12
6-11 yrs of age

Mean ± 95% CI
Adjusted CRD, exclusion of missing data, ITT
ED ≥ 1000 mg and ≥ 10-fold increase of the ED at Month 12
6-11 yrs of age

Viaskin Peanut dose-response effect on a more stringent criteria
Change from baseline Peanut- sIgE & sIgG4
6-11 yrs of age

Peanut-specific IgE (kU$_A$/L)

Peanut-specific IgG4 (mg/L)

Viaskin Peanut 250 µg, n=28
Viaskin Peanut 100 µg, n=26
Viaskin Peanut 50 µg, n=28
Placebo, n=31

Median ± IQR
Exclusion of missing data, ITT
Increasing the stringency of the responder definition

VIPES Criterion

New Criterion

<table>
<thead>
<tr>
<th>Eliciting Dose at baseline</th>
<th>Eliciting Dose at M12</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 30 mg</td>
<td>&gt; 300 mg</td>
</tr>
<tr>
<td>&gt; 30 mg</td>
<td>&gt; 1000 mg</td>
</tr>
</tbody>
</table>
Treatment Responders at Month 12, New criterion
6-11 yrs of age

- Placebo: 12.9% (n = 31)
- 50 μg: 39.3% (n = 28)
- 100 μg: 42.3% (n = 26)
- 250 μg: 50.0% (n = 28)

Significance levels:
- p = 0.0346
- p = 0.0166
- p = 0.0039
EPIT® with Viaskin Peanut: Conclusions

- VIPES: largest, multicenter RCT in peanut allergy
- Excellent compliance
- Appears safe in all populations
- Met primary efficacy endpoint
- In children’s subgroup: statistical efficacy demonstrated for all doses
  - Dose effect on the cumulative reactive quantity of peanut
  - Stronger magnitude for 250 µg
- In adolescent and adult subgroups: higher response rate with Viaskin Peanut 250 µg, but was a magnitude lower than in children
Epicutaneous Immunotherapy: A Promising Therapeutical Approach for Eosinophilic Esophagitis

by Dr. Jonathan Spergel, Children Hospital, Philadelphia (USA)
Viaskin® Milk – Treating Milk induced Eosinophilic Esophagitis

Jonathan M. Spergel, MD, PhD
Division of Allergy and Immunology
The Children’s Hospital of Philadelphia
Perelman School of Medicine at Univ. of Pennsylvania
World Map of Eosinophilic Esophagitis (EoE)
Rise of EoE

- Incidence in US in 3 separate studies
  - 1/2000
- However, may be higher
  - Random endoscopy/biopsy-1/100
**EoE Symptoms**

Comparison of patient-reported EoE symptoms, by age

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Children*</th>
<th>Teenagers</th>
<th>Adults</th>
</tr>
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<tbody>
<tr>
<td>Failure to thrive</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty feeding/food refusal</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chest pain</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dysphagia</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Overchewing food</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Overcutting food</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Impaction</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

EoE, Eosinophilic esophagitis.

*Additional symptoms may be suspected but not verbalized.
EoE as a Progressive Disease

Dellon et al. Gastrointest Endosc. 2013

OR = 2.1 (1.7-2.7) per 10 year increase for developing a fibrostenotic EoE phenotype
EoE

Allergic Insult + GERD
Genetic Risk Factor

IL-33
TSLP
IL-13
IL-5
IL-9
POSTN
CCL26
desmoglein-1

barrier function
proliferation
fibrosis
mastocytosis
eosinophilia

eosinophil
dendritic cell
Th2 cell
fibroblast
epithelial cells
mast cell
basophil
ILC-2
EoE ≠ IgE Mediated Disease

EoE diagnosis
- Educate family on options

Nutrition Therapy
- Elimination diet
- Combination: Elimination diet with Elemental supplementation
- Elemental diet

Pharmacologic Therapy
- Combination of Diet and Steroids
- Steroids: Topical or Systemic

Dilation
Pharmacologic Therapy

**Systemic Steroids** – effective at improving symptoms and histology of EoE in 95% of pts
  - Upon discontinuation, 90% had recurrence of symptoms
  - *(Long term use) Side effects*: bone abnormalities, poor growth, adrenal suppression
  - May be needed short term for extreme cases

**Topical/swallowed Steroids** – less toxic to pt while still 50-85% effective
  - A mainstay of EoE treatment in adults and children.
  - Upon discontinuation almost all patients have a recurrence of symptoms
  - Often, large doses needed
  - *Side effects*: esophageal candidiasis

Liacouras *et al*. Clin Gastroenterol Hepatol 2005
Furuta *et al*. Gastroenterology 2007
Food Avoidance Therapy
Food Allergy and EoE

• Kelly and Sampson
  • 10 patients (5 yr, range: 8 mo-12.5 yr)
  • Endoscopy pre- & post-trial

Kelly et al. Gastroenterology 1995

• Gonsalves
  • Food Reintroduction

Gonsalves et al. Gastroenterology 2012
Oral Immunotherapy induces EoE

- Seen after egg, milk and peanut OIT
- Incidence about 10-20%
- Indicates foods causes EoE and it is not a TH2 mechanism

Ridolo et al. Ann Allergy, Asthma & Immunology 2011
Silvers et al. J Allergy Clin Immunol 2014
The Idea

EoE is a food mediated disease
  • Not IgE mediated

Milk in the primary allergy
  • Seen >70%

No Cure for EoE
  • Avoidance
  • Treating Symptoms

EPIT® for desensitization!!!
Murine and Pig EoE

- Induced in multiple models
- Not-IgE mediated
- “Cured” by EPIT for mice and pig
In Vivo POC: Sensitized Mice Exposed to peanut regimen Inducing Esophageal Eosinophilia

**SENSITIZATION**
peanuts + Cholera toxin (6 ig* for 6 weeks)

**IMMUNOTHERAPY**
EPIT 100
Sham
Naive

**10-DAY-PEANUT-REGIMEN**
Sampling: Spleen (cell culture) Esophagus (histology, mRNA analysis)

Mondoulet *et al.* PLoS One, 7(2): e31967
In Vivo POC: Observed Efficacy on Challenged Esophageal Tissue

Expressed as eosinophils/mm²


Mondoulet et al. PLoS One, 7(2): e31967
Skin Morphology: **Animal Models vs Humans**

- **Pig skin is structurally similar to human skin**
- **Pig skin is constituted of dermal hair follicles as in Humans**
EPIT® for Eosinophilic Digestive Disorders

SENSITIZATION TO PEANUTS

Daily peanut oral exposure + standard food

N=8

FIBROSCOPY

IMMUNOTHERAPY

D1

D49

D58

D60

D150

D159

D160

D162

Daily peanut oral exposure + standard food

N=8

EPIT 100

Placebo

Control

FIBROSCOPY

END OF STUDY

Illustrations endoscopy observations

Control

Placebo

EPIT

Ulcer

Mondoulet et al. EAACI 2013
Efficacy of EPIT® in Eosinophilic Digestive Disorders

Stomachal samplings blindly analyzed by histology

EPIT decreases eosinophilic infiltration in stomach

Mondoulet et al. EAACI 2013
SMILEE study

A double-blind, placebo-controlled, randomized trial to study efficacy and safety of the Viaskin® MILk for treating Milk Induced Eosinophilic Esophagitis in children
SMILEE Study Design

• 20 subjects (4-17 years of age)
• Randomization 3:1 (15 Viaskin Milk: 5 Placebo)
• EPIT treatment starts at randomization.
• Re-introduction of milk after 9 months of EPIT®
• Biopsy while on milk at the end of treatment (up to Month 11)
SMILEE Summary Design

Milk Exposure*  | Milk-Free Diet  | Milk Exposure*

Upper Endoscopy/Biopsy

V1  V2  V3  

D1  D8

V4  V5  

V6  M1

V7  M3

V8  M6

V9  M9

V10  up to M11

V11  2 weeks after V10

Randomization
Start Treatment

Milk reintroduced

Primary Endpoint

*Milk Exposure is 1 week to 2 Months
Conclusion

• EoE is debilitating and rising
• Milk involved in > 70% cases of EoE

EPIT® promising to treat Cow’s Milk induced EoE
Following our Symposium we are pleased to welcome you to a Cocktail Party at the Hilton Diagonal Mar from 7:00 to 10:00 pm