What’s Hot and Happening in the Cosmetics World

Jill C Fichtel, MD
CEO and Owner, Transformative Dermatology
Franklin, Tn
Conflicts of Interest / Disclosures

Viveve, Evolus, Prollenium, Alma, BTL, Omni, Prescribers Choice, Ortho, Aerolase, Strathspey Crown, Alphaeon
Neurotoxin Update
Jeuveau™

Just another botulinum toxin?
PrabotulinumtoxinA-xvfs for injection

INDICATIONS AND USAGE

- PrabotulinumtoxinA-xvfs is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients

  - 2.5 mL diluent added to 100U vial
  - 20 unit dose
  - 5 point injection pattern

1. Jeuveau Package Insert Section 1.1
2. Jeuveau Package Insert Section 2
PrabotulinumtoxinA-xvfs

Starting Ingredients\(^1,2\)

Source Organism
*C. botulinum* producing A1 botulinum toxin

Active Ingredient
Botulinum toxin type A1
900kDa, full complex

<table>
<thead>
<tr>
<th>Role</th>
<th>Material</th>
<th>Content (per vial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stabilizing Agent(^1)</td>
<td>Human Serum Albumin, HSA</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Isotonic Agent(^1)</td>
<td>Sodium Chloride, NaCl</td>
<td>0.9 mg</td>
</tr>
<tr>
<td>Active(^1)</td>
<td>C. Botulinum Toxin Type A</td>
<td>100 units</td>
</tr>
</tbody>
</table>

1. Jeuveau Package Insert Section 2.2, Section 11
**PrabotulinumtoxinA-xvfs for injection**

>2,100 Patients Across Five Clinical Trials

<table>
<thead>
<tr>
<th>Phase III Studies</th>
<th>Phase II Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US EV-001 and EV-002</strong></td>
<td><strong>Europe / Canada EVB-003</strong></td>
</tr>
<tr>
<td>- Two identical Phase III studies</td>
<td>- EVB-003</td>
</tr>
<tr>
<td>- N= 330 EV-001, N= 324 EV-002</td>
<td>- N=540</td>
</tr>
<tr>
<td>- Superiority to placebo</td>
<td>- Non-Inferiority to onabotulinumtoxinA</td>
</tr>
<tr>
<td>- Vacuum dried formulation</td>
<td>- Superiority to placebo</td>
</tr>
<tr>
<td></td>
<td>- Vacuum dried formulation</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>US EV-004</strong></td>
<td><strong>US EV-006</strong></td>
</tr>
<tr>
<td>- Open-label, repeat-tx, safety</td>
<td>- Open-label, repeat-tx, safety</td>
</tr>
<tr>
<td>- N= 352</td>
<td>- N=570 formulation</td>
</tr>
<tr>
<td>- Freeze dried formulation</td>
<td>- Vacuum dried formulation</td>
</tr>
</tbody>
</table>

Data on file CSR’s EV-001, EV-002, EVB-003, EV-004 EV-006
PrabotulinumtoxinA-xvfs
Europe and Canada Phase III Trial
A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Single-Dose, Phase III, Non-Inferiority Study Comparing PrabotulinumtoxinA and OnabotulinumtoxinA for the Treatment of Moderate to Severe Glabellar Lines in Adult Subjects

Berthold-Josef Rzany, MD, ScM, Benjamin Ascher, MD, Rui L Avelar, MD, Jesper Bergdahl, MD, Vince Bertucci, MD, Isaac Bodokh, MD, James Alastair Carruthers, MD, Hugues Cartier, MD, Henry Delmar, MD, Ralf Denfeld, MD, John E Gross, MD, FACS, Marc Heckmann, MD, Per Hedén, MD, Said Hilton, MD, Christopher Inglefield, MD, Patricia Ogilvie, MD, Gerhard Sattler, MD, Michael Sebastian, MD, Nowell Solish, MD, Arthur Swift, MD, Patrick Trévidic, MD


Published: 05 April 2019  Article history v
Europe and Canada Phase III Trial
Glabellar Line Study Design

Study Design
Multi-center, blinded, randomized, single dose study
N = 540,
Randomized 5:5:1 (Prabot:Onabot:Placebo)

Study Population
Subjects ≥18 years of age
Moderate (GLS=2) to severe (GLS=3)
Glabellar lines had an important psychological impact
(on mood, anxiety and/or depressive symptoms)

Primary Endpoint
GLS= 0 or 1 at Day 30 by Investigator Assessment
Non-inferiority

Europe and Canada Phase III Trial
Primary Endpoint: Non-inferiority Met

Primary Endpoint
Responder Rate Day 30
GLS = 0 or 1 at Maximum Frown Investigator Assessment

- Difference between groups: 4.4%
- Lower limit of one-sided 97.5% CI: -1.9%
- Non-inferiority margin: -10%

Jeuveau™
n=235
87.2

Botox
n=244
82.8

Placebo
n=48
4.2

Favors Onabot
Favors Prabot-xvfs

Lower Limit of two-sided 95% CI: -1.9%
Upper Limit of two-sided 95% CI: 10.8%

Europe and Canada Phase III Trial

Secondary Endpoints

≥1 Improvement GLS at Maximum Frown

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Onabot</th>
<th>Prabot-xvfs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 2</td>
<td>12.20%</td>
<td>57.00%</td>
<td>54.2%*</td>
</tr>
<tr>
<td>Day 150</td>
<td>8.30%</td>
<td>34.40%</td>
<td>37.7%*</td>
</tr>
</tbody>
</table>

Investigator Assessment

Subject Satisfaction

≥1 Improvement Subject Satisfaction

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Onabot</th>
<th>Prabot-xvfs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 30</td>
<td>6.30%</td>
<td>86.60%</td>
<td>91.3%*</td>
</tr>
</tbody>
</table>

Source: Data on file (CSR EVB-003, pg 6)
Europe and Canada Phase III Trial
Secondary Endpoints

- HADS, Hospital Anxiety Depression Scale
  - Developed to detect states of depression, anxiety and emotional distress
  - Scale has 7 depression questions and 7 anxiety questions

### Hospital Anxiety and Depression Scale DWP-450 vs Baseline Score at Day 90

<table>
<thead>
<tr>
<th></th>
<th>Anxiety</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HADS, All (Day 90)</strong></td>
<td>Placebo</td>
<td>Onabot</td>
</tr>
<tr>
<td>Mean Change ±SD</td>
<td>−0.9</td>
<td>−0.9</td>
</tr>
<tr>
<td><em>P</em>-Value vs baseline</td>
<td>&lt;0.013</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Europe and Canada Phase III Trial
Exploratory Endpoint

Prabot-xvfs vs Onabot
≥1 Pt Improvement of GLS at Maximum Frown

![Graphs showing investigator and subject assessment of GLS improvement over different days post-treatment for Jeuveau™, Botox, and placebo.](image)
Europe and Canada Phase III Trial
Exploratory Endpoint

**Prabot-xvfs vs Onabot**
Global Aesthetic Improvement Scale

<table>
<thead>
<tr>
<th>Days Post Treatment</th>
<th>Investigator Assessment</th>
<th>Subject Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Responders on the GAIS (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jeuveau™</td>
<td>Botox</td>
</tr>
<tr>
<td>2</td>
<td>60.1</td>
<td>8.3</td>
</tr>
<tr>
<td>14</td>
<td>96.6</td>
<td>8.5</td>
</tr>
<tr>
<td>30</td>
<td>96.7</td>
<td>4.2</td>
</tr>
<tr>
<td>90</td>
<td>81.9</td>
<td>6.3</td>
</tr>
<tr>
<td>120</td>
<td>69.8</td>
<td>2.1</td>
</tr>
<tr>
<td>150/ET</td>
<td>49.6</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Days Post Treatment

**Europe and Canada Phase III Trial**
**Exploratory Endpoint**
Europe and Canada Phase III Trial
Exploratory Endpoint

Prabot-xvfs vs Onabot

Subject Satisfaction

Source: Data on file (CSR EVB-003, pg 89)
PrabotulinumtoxinA EU/CA Phase III Trial

No Drug Related Serious Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event Parameter</th>
<th>Prabot (N=245)</th>
<th>Onabot (N=246)</th>
<th>Placebo (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)</td>
<td>Events</td>
</tr>
<tr>
<td>Any AEs</td>
<td>92</td>
<td>(37.6)</td>
<td>152</td>
</tr>
<tr>
<td>Incidence diff., % (95% CI)</td>
<td></td>
<td></td>
<td>4.3</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>3</td>
<td>(1.2)</td>
<td>6</td>
</tr>
<tr>
<td>Any study drug-related AE</td>
<td>38</td>
<td>(15.5)</td>
<td>46</td>
</tr>
<tr>
<td>Incidence diff., % (95% CI)</td>
<td></td>
<td></td>
<td>3.7</td>
</tr>
<tr>
<td>Any study drug-related AE of special interest</td>
<td>5</td>
<td>(2.0)</td>
<td>5</td>
</tr>
<tr>
<td>Any AE leading to study discontinuation</td>
<td>0</td>
<td>(0.0)</td>
<td>0</td>
</tr>
<tr>
<td>Any AE leading to death</td>
<td>0</td>
<td>(0.0)</td>
<td>0</td>
</tr>
<tr>
<td>Any AE with frequency ≥ 5%</td>
<td>52</td>
<td>(21.2)</td>
<td>59</td>
</tr>
<tr>
<td>Nervous system disorder, headache</td>
<td>34</td>
<td>(13.9)</td>
<td>38</td>
</tr>
<tr>
<td>Incidence diff., % (95% CI)</td>
<td></td>
<td></td>
<td>3.7</td>
</tr>
<tr>
<td>Infections and infestations, nasopharyngitis</td>
<td>21</td>
<td>(8.6)</td>
<td>21</td>
</tr>
<tr>
<td>Incidence diff., % (95% CI)</td>
<td></td>
<td></td>
<td>-2.8</td>
</tr>
</tbody>
</table>

Source: Data on file (CSR EVB-003 p 112, 114, 116)
## PrabotulinumtoxinA EU/CA Phase III Trial

Summary of Adverse Events Occurring with a Frequency of \( \geq 1\% \) in Either the Prabot or Onabot Groups (Safety Population)

<table>
<thead>
<tr>
<th>System organ class and preferred term</th>
<th>Prabot (N=245)</th>
<th>Onabot (N=246)</th>
<th>Placebo (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>34 (13.9)</td>
<td>25 (10.2)</td>
<td>7 (14.3)</td>
</tr>
<tr>
<td>Muscle tone disorder</td>
<td>3 (1.2)</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>1 (0.4)</td>
<td>3 (1.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Influenza</td>
<td>3 (1.2)</td>
<td>5 (2.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>21 (8.6)</td>
<td>28 (11.4)</td>
<td>2 (4.1)</td>
</tr>
<tr>
<td>Oral herpes</td>
<td>3 (1.2)</td>
<td>4 (1.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>3 (1.2)</td>
<td>1 (0.4)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyelid ptosis</td>
<td>4 (1.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Eyelid sensory disorder</td>
<td>0 (0.0)</td>
<td>4 (1.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (0.4)</td>
<td>3 (1.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>1 (0.4)</td>
<td>3 (1.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>3 (1.2)</td>
<td>4 (1.6)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contusion</td>
<td>0 (0.0)</td>
<td>3 (1.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Procedural headache</td>
<td>3 (1.2)</td>
<td>2 (0.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (0.4)</td>
<td>4 (1.6)</td>
<td>1 (2.0)</td>
</tr>
</tbody>
</table>

Source: Data on file (CSR EVB-003 p 112, 114, 116)
## Safety Profile: Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>EVB-003</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>All</td>
<td>32.7%</td>
</tr>
<tr>
<td>Related</td>
<td>4.1%</td>
</tr>
</tbody>
</table>

### Serious Adverse Events (SAE’s)
- Drug Related
  - None

### Other AE’s of Interest
- Ptosis (related)
  - Eyelid – Prabot-xvfs 1.6%, Onabot 0%
  - Eyebrow – Prabot-xvfs 0%, Onabot 0.4%

### Most Common AEs (≥5%)
- Headache
  - (14.3% Placebo, 10.2% Onabot, 13.9% Prabot-xvfs)
- Nasopharyngitis
  - (4.1% Placebo, 11.4% Onabot, 8.6% Prabot-xvfs)
Early Experience with PrabotulinumumtoxinA

- J.E.T. Program Survey
  - Over 28,000 consumers completing surveys after treatment:
    - Approximately 25% were toxin naïve
    - High rates of satisfaction at day 90
      - High willingness to recommend it to a friend
My Early Experience with Probat

• Treated my first patient approximately 4 months ago
• Have treated around 50 patients so far
• Initial Impressions:
  • “Kicks In” in around 48-72 hours
  • Seems to start working consistently in all areas
  • When near the minimum necessary dose for the frontalis, seems to be a “Peak, dip and plateau” (Sharon Stokes, FAAD – Orlando, Fl)
Frontalis Considerations

• NO ‘cookie cutter’ approach, regardless of which toxin used
  • Highly variable anatomy that changes over time, leading to changes in placement needs
  • Dose range can vary by 10x, from as little as 3 units to as much as 30
  • Patient may want some movement vs lots vs none
    • “Trade off” of softening line above brow vs more movement of brow
  • Recruiting frontalis to elevate eyelids
  • Thickening of dermis and depth of injection
  • Physical activity
  • Product variability from lot to lot
  • Wash out
Probat in Frontalis

- For a patient having frontalis treated with Probat for the first time:
  - Inject using same technique and dosing you would have used for Ona
  - Recheck/touch-up in two weeks
    - This is my standard protocol after any frontalis treatment
  - Recheck again in 4 weeks after that (6 weeks after initial injection)
Off Label / Advanced Use of Neurotoxins

• Upper face
  • Correct ‘heavy’ brow
    • Whether natural or toxin induced
    • Whether medial brow or arches of brow
  • Widening of ocular aperture to equalize asymmetry or make the eyes appear larger
  • Bunny lines
Off Label / Advanced Use of Neurotoxins

• Lower face
  • Nasal sling
  • Gummy smile, uneven smile
  • Lip lines (lip flip)
  • DAO lines
  • Prominent mentalis (peau d’orange)
  • Trigeminal neuralgia
  • TMJ
  • Facial shaping, masseter hypertrophy
Off Label / Advanced Use of Neurotoxins

• Neck
  • Nefertiti neck lift
  • Neck bands (medial and lateral)
Filler Update
versa™

Just another cross-linked HA filler?
PRODUCT CHARACTERISTICS

- Versa™ is composed of BDDE-cross-linked HA gel, milled and combined with 10% unmodified HA, then dialyzed against PBS (phosphate buffered saline), filled in 1-ml syringes, and terminally-sterilized in an autoclave by moist heat.

- The particles are uniquely spherical and uniform, providing a balance between smoothness and volume.

- 25mg/mL of HA

- 7% cross linking (Juvederm® Ultra Plus 11%, Restylane® 1.2%)

- Versa™ is a homogenous filler due to an advanced wet milling technology and proprietary formula.

- Revanesse® Versa™ is designed to be balanced with the water content of natural skin tissue.

- The product doesn’t release or absorb surrounding water.
GEL PARTICLE SHAPE

Juvéderm® Ultra Plus is a registered trademark of Allergan. Revanesse® Versa™ is a registered trademark of Prollenium Medical Technologies Inc. Restylane® is a registered trademark of Galderma Laboratories, L.P.
The particles in Restylane® have a different character than those of Revanesse® Versa™ and Juvederm® Ultra Plus.

The particles are more irregular, and elongated, and appear ‘harder’ with sharper edges.

This may be a result of the proprietary ‘double’ cross-linking process used by Q-med, which is intended to produce a degree of ‘physical’ cross-linking.

This is supported by higher values of the storage modulus, G’, seen with this filler.
The particles in Revanesse® Versa™ and Juvederm® Ultra Plus are similar.
- Approximately the same size
- Revanesse® particle is more round and spherical
The aspect ratio measures how spherical a particle is. To be a perfect sphere, the length and width of the particle should match. Following this method, the aspect ratio of a perfect sphere is 1.0. The batch of Revanesse® VersaTM tested for this study was composed of over 68% perfectly spherical particles.
GEL PROPERTIES
EXTRUSION FORCE

<table>
<thead>
<tr>
<th>Product</th>
<th>Exrusion Force/LB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revanesse® Versa™</td>
<td>3</td>
</tr>
<tr>
<td>Restylane®</td>
<td>1</td>
</tr>
<tr>
<td>Juvederm® Utra Plus</td>
<td>5.1</td>
</tr>
<tr>
<td>Juvéderm® Ultra</td>
<td>2.7</td>
</tr>
</tbody>
</table>

BDDE Cross-linked Hyaluronan Dermal Fillers Comparison of Commercial Products Update Report RD045
The most important effect of cross-linking is to increase the durability of the filler.

It also has an effect on the degree to which the filler absorbs water after implantation.

Excessive cross-linking can lead to a hard implant with an unacceptable incidence of adverse reactions.

The most basic parameter describing the degree of cross-linking is the overall concentration of BDDE link molecules per disaccharide unit of HA in the gel.

The advanced crosslinking process is designed to promote links between different HA polymer chains and to minimize less effective links on parts of the same chain.*

* M.H. Gold, Stafford Baumann, C.P. Clark III, J. Schlessinger
PERCENTAGE CROSS-LINKING

M.H. Gold, Stafford Baumann, C.P. Clark III, J. Schlessinger
US PIVOTAL STUDY
background

• Designed as a non-inferiority study vs Restylane®
• Set up to reveal the safety profile of Revanesse® Versa™
• The FDA defined the primary endpoint of 24 weeks
• Qualified subjects had NLFs with a wrinkle severity rating scale (WSRS) score of 3 or 4 (moderate or severe)
• NLFs were treated with Versa™ on one side of the face and Restylane® on the other side
• Side of the face for each product was randomly assigned
• Evaluating investigator and subject were blinded and injections were performed by unblinded physician
• Maximum of 2mL per fold
• All initial treatments were administered at baseline in addition to WSRS, evaluations included the global aesthetic improvement scale (GAI) of the investigator and the patients as well as adverse events recorded in a diary of each subject

• Based on use of photographs, the WSRS is designed to quantify facial folds by visual assessment of the length and apparent depth of the fold without referring to baseline
• In contrast, the GAI scale is used to grade overall improvement in each fold by comparing its appearance at follow up against a high magnification photograph taken before treatment
• For subjects not requiring retreatment, the study period ended at week 24
PRIMARY EFFICACY ENDPOINT

Mean Change from Baseline at 24 weeks

<table>
<thead>
<tr>
<th></th>
<th>N = 125</th>
<th>P &lt; 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revanesse® Versa™</td>
<td>1.02</td>
<td>±0.692</td>
</tr>
<tr>
<td>SD=1.09±0.692</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restylane®</td>
<td>0.91</td>
<td>±0.746</td>
</tr>
<tr>
<td>SD=0.95±0.746</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gold, M. A Multicenter, Double-Blinded, Randomized, Split-Face Study of the Safety and Efficacy of a Novel Hyaluronic Acid Gel For the Correction of Nasolabial Folds. Data on File.
SECONDARY EFFICACY VARIABLES OF TREATMENT SUCCESS

<table>
<thead>
<tr>
<th>Treatment Success</th>
<th>iGAI (Investigator Global Aesthetic Improvement) Change from Baseline</th>
<th>pGAI (Patient Global Aesthetic Improvement) Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=125</td>
<td>N=124</td>
<td>N=124</td>
</tr>
<tr>
<td>Revanesse® Versa™</td>
<td>78.4</td>
<td>59.2</td>
</tr>
<tr>
<td>Restylane®</td>
<td>72.8</td>
<td>47.2</td>
</tr>
<tr>
<td></td>
<td>44.4</td>
<td>30.6</td>
</tr>
</tbody>
</table>

Gold, M. A Multicenter, Double-Blinded, Randomized, Split-Face Study of the Safety and Efficacy of a Novel Hyaluronic Acid Gel For the Correction of Nasolabial Folds. Data on File.
PERCENTAGE OF TEST PATIENTS REPORTED SWELLING

Gold, M. A Multicenter, Double-Blinded, Randomized, Split-Face Study of the Safety and Efficacy of a Novel Hyaluronic Acid Gel For the Correction of Nasolabial Folds. Data on File.
SAFETY
Treatment-emergent adverse events

- No subjects discontinued the study due to AE
- TEAEs were reported for 69.9% of Revanesse® Versa™ subjects vs. 84% of Restylane® subjects
- Most common injection site TEAEs were:
  - Hematoma (50.3% versa™ / 47.2% Restylane®)
  - Swelling (47.2% versa™ / 71.2% Restylane®)
  - Pain (38% versa™ / 66.3% Restylane®)
- Only 2 subjects reported non-injection site TEAEs (headache 3.1%, arthralgia 1.85)

Gold, M. A Multicenter, Double-Blinded, Randomized, Split-Face Study of the Safety and Efficacy of a Novel Hyaluronic Acid Gel For the Correction of Nasolabial Folds. Data on File.
Advanced Filler areas

- Forehead
- Ocular area
- Oral area
- Nose
- Jawline
- Chin
Body Sculpting Update
Muscle Sculpting Market Opportunity

**Fitness is a Huge Business**

- $595 Billion¹
- $532 Billion²
- $355 Billion³
- $125 Billion⁴
- $84 Billion⁵

Global Wellness Economy (Beauty, Fitness, Nutrition) projected to grow faster than Gross Domestic Product.

**Driven by Strong Psychological Beliefs**

- 79% of Americans report feeling unhappy with how their body looks.
- 88% of women and 65% of men influenced by body images that they see in the media.

**But a Large Gap Between Desires and Results Remains**

- 60 Million Health Club Members
- 30% of adults engage in the recommended amount of weight training (2x/week).

• Trusculpt Flex
  • Electrical stimulation of muscle
• EmSculpt
  • Magnetic stimulation of muscle
• BeautyFill
  • Integrated Liposuction/Fat Transfer System
ELECTRICAL MUSCLE STIMULATION

Electrical muscle stimulation (EMS)

• Used for muscle strengthening in physiotherapy and sport science

• Limitations:
  ▪ Electrical current finds the shortest path between the electrodes. Most of the energy concentrates in superficial layers, only part of it reaches the muscle.
  ▪ Intensity is limited due to pain and risk of burns.
3 Main Categories of Bio-Electrical Muscle Stimulation

- Transcutaneous Electrical Nerve Stimulation (TENS)
- Traditional Electrical Muscle Stimulation (EMS)
- truSculpt flex Multi-Directional Stimulation (MDS)
Transcutaneous Electrical Nerve Stimulation

- Stimulation of superficial nerves with <1 mA
- Induces a “flicking” effect on the muscles
- Appropriate for management of pain and inflammation
Traditional EMS Mechanism Of Action

Electrical Muscle Stimulation

• Stimulation of the superficial muscle with <10 mA
• Induces a single direction slight muscle contractions
• Generally used for muscle rehabilitation to reduce atrophy from injury
The truSculpt flex Improvement

• truSculpt flex differs from previously existing EMS systems via:
  • Updated treatment modes & protocols
  • Enhanced power supply
  • Channels operate independently and simultaneously
  • Increased power delivery to muscle with truSculpt handpieces and truGel
  • Even energy delivery allowed delivery of 2-3 X more current to the muscle
  • Intuitive user interface
  • Retractable cables
Bio-Electrical Muscle Stimulation
• Direct vs indirect stimulation for high intensity and specificity with 30 mA
• Changes polarity or direction

truControl™
• Targets selective muscles, customize current delivery (intensity and direction)

Multi-Directional Stimulation (MDS)
• Offers three treatment mode options
• Creates multiple types of muscle contractions
• Treats up to 8 areas per session
Clinical Data

*All patients maintained weight within +/- 5%
truSculpt flex Results

Before
4 Weeks After 4 Txs
8 Weeks After 4 Txs
12 Weeks After 4 Txs
truSculpt flex Results

Before  truSculpt® flex  8 Weeks After 4 Txs

Photos courtesy of S. Ronan, M.D.
truSculpt flex Results

Before

12 Weeks After 6 Tx

Photos courtesy of S. Ronan, M.D.
truSculpt flex Ultrasound Results
Emsculpt
High-Intensity Focused Electromagnetic Energy

• Rapidly changing magnetic fields induce currents in the tissue.
• This leads to depolarization of motor neurons in the treated area—> muscle contraction
• The focused energy induces 20,000 muscle contractions in 30 min
• This results in so-called supramaximal contractions that can never be achieved through normal voluntary muscle action
HIFEM MUSCLE STIMULATION

- HIFEM uses secondary current induced by magnetic fields. **Current density peaks in the muscle, not skin.** This allows extremely intense stimulation.

- EMS/TENS systems use direct superficial electricity which limits their intensity.
Autonomous brain reserve
Untrained individual can only activate 40-60% of muscle potential.

CNS pathways limitations
The intensity of electrical signaling from the brain has certain limits.

Complete tetanic state
Voluntary exercise doesn’t allow such high frequency of contractions which is needed to achieve maximum tension in the muscle.

HIFEM is independent of the brain function and so bypasses these limitations.
<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>TYPE</th>
<th>TITLE</th>
<th>SAMPLE</th>
<th>PUBLISHED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacob et al</td>
<td>Tummy; Tape</td>
<td>Safety and efficacy of a novel HIFEM technology device for noninvasive abdominal body shaping</td>
<td>22</td>
<td>JCD 2018</td>
</tr>
<tr>
<td>Kinney et al</td>
<td>Tummy; MRI</td>
<td>HIFEM Therapy Evaluated by Magnetic Resonance Imaging: Safety and Efficacy Study of a Dual Tissue Effect Based Non-Invasive Abdominal Body Shaping</td>
<td>22</td>
<td>LSM 2018</td>
</tr>
<tr>
<td>Weiss et al</td>
<td>Pigs; Histology</td>
<td>Induction of Fat Apoptosis by a Non-Thermal Device: Mechanism of Action of Non-Invasive HIFEM Technology in a Porcine Model</td>
<td>3</td>
<td>LSM 2018</td>
</tr>
<tr>
<td>Multicenter (?)</td>
<td>Butt; BA &amp; Satisfaction</td>
<td>HIFEM Technology for Non-Invasive Buttock Lifting and Toning of Gluteal Muscles: A Multi-Center Efficacy and Safety Study</td>
<td>75</td>
<td>JDD 2018</td>
</tr>
<tr>
<td>Kent et al</td>
<td>Tummy; CT</td>
<td>Computed Tomography (CT) Based Evidence of Simultaneous Changes in Human Adipose and Muscle Tissues Following a HIFEM Application: A New Method for Noninvasive Body Sculpting</td>
<td>25</td>
<td>ASLMS 2018</td>
</tr>
<tr>
<td>Busso et al</td>
<td>Butt; Tx feasibility</td>
<td>Efficacy of HIFEM Field Therapy when Used for Non-Invasive Buttocks Augmentation and Lifting: A Clinical Study</td>
<td>22</td>
<td>ASLMS 2018</td>
</tr>
<tr>
<td>Katz et al</td>
<td>Tummy; Ultrasound</td>
<td>Ultrasound Assessment of Subcutaneous Abdominal Fat Thickness Following Treatments with HIFEM Field Device: A Multi-Center Study</td>
<td>33</td>
<td>DS 2019 (accepted)</td>
</tr>
<tr>
<td>Duncan et al</td>
<td>Leg; Histology</td>
<td>Non-Invasive Induction of Muscle Fiber Hypertrophy and Hyperplasia: Effects of HIFEM Field Evaluated in an In Vivo Porcine Model</td>
<td>4</td>
<td>ASLMS 2019</td>
</tr>
<tr>
<td>Kent et al</td>
<td>Tummy; CT&amp;MRI</td>
<td>Long-Term Follow-Up on Patients with HIFEM-Induced Abdominal Tissue Changes: MRI and CT Assisted Quantification of Muscle Growth and Fat Reduction</td>
<td>21</td>
<td>ASLMS 2019</td>
</tr>
<tr>
<td>Katz et al</td>
<td>Tummy; Ultrasound</td>
<td>Ultrasonography Evaluation of Changes in Subcutaneous Abdominal Fat Thickness Following HIFEM Treatments: Results of 6-Month Follow-Up</td>
<td>18</td>
<td>ASLMS 2019</td>
</tr>
<tr>
<td>Palm et al</td>
<td>Butt; MRI</td>
<td>MRI Evaluation of Changes in Gluteal Muscles Following Treatments with the HIFEM Technology</td>
<td>25</td>
<td>ASLMS 2019</td>
</tr>
<tr>
<td>Halaas et al</td>
<td>Tummy; Histology</td>
<td>Biochemical Perspective of Fat Physiology after Application of HIFEM: Field Technology: Additional Investigation of Fat Disruption Effects in a Porcine Study</td>
<td>3</td>
<td>ASLMS 2019</td>
</tr>
<tr>
<td>A. Fatemi</td>
<td>Tummy; Ultrasound</td>
<td>An ultrasound evaluation of HIFEM technology for fat reduction: case study</td>
<td>7</td>
<td>IMCAS PARIS 2019</td>
</tr>
<tr>
<td>R. Rakus</td>
<td>Literature; Efficacy</td>
<td>Thermal vs. non-thermal technologies in non-invasive body contouring</td>
<td>n/a</td>
<td>IMCAS PARIS 2019</td>
</tr>
</tbody>
</table>

**PEER-REVIEWED RESEARCH**

**9 MONTHS AFTER INTRODUCTION TO THE MARKET**
PRIMARY EFFECTS ON THE MUSCLES

Supramaximal contractions induce microinjury & trigger muscle growth.

RESEARCH SO FAR

23% increase in muscle mass density
  • 16% hypertrophy
  • 7% hyperplasia

19-23% abdominal muscle thickening

11% increase in total volume of all three gluteal muscles

10-11% reduction in abdominal separation / diastasis recti

Measureable improvement preserved 6-12 months post treatments

Effects of HIFEM on myo-satellite cells is still subject of investigation
In certain concentrations, free fatty acids (FFA) were proven to have apoptosis inducing effects (Hardy et al 2013; Zhang 2012; Gunduz et al 2012; Guo et al 2007).

HIFEM induced contractions lead to a hypermetabolic state with a rapid release of FFA in fat tissue (Weiss 2018).

A statistically significant increase in fat apoptotic levels was measured (Weiss 2018) as well as an increase in mRNA apoptotic markers (Weiss 2018).

Reduction in subcutaneous fat thickness was successfully observed in patients (Kent 2018; Kinney 2018; Katz 2018; Jacob 2018).

SECONDARY EFFECTS HAPPEN IN ADIPOSE TISSUE
Brown marked are cells with initiated DNA breakdown. The # apoptotic cells increased post application. The average apoptotic index increased from 18.8% before application to 35.9% after application.

In the treated area, the concentration of FFA in fat tissue rapidly increased immediately after the treatment.

Brown marked are cells with initiated DNA breakdown. The # apoptotic cells increased post application.
AVERAGE 19-27% REDUCTION IN FAT MEASURED IN PATIENTS

Reduction in subcutaneous fat following a series of HIFEM treatments. 3D photography shows consistent reduction of fat across the abdomen.

CT scan shows reduction in subQ fat approximately 6 weeks after a series of treatments.

MRI scan of a patient with visible fat pad reduction 2 months after the last treatment.
AVERAGE 19-27% REDUCTION IN FAT:
AN ULTRASOUND EVIDENCE
PATIENTS SEEKING IMPROVEMENT IN BOTH MUSCLE & FAT

BEFORE | 12 WEEKS AFTER 4th TREATMENT | BEFORE | AFTER 4th TREATMENT

BEFORE | AFTER 4th TREATMENT

BEFORE | AFTER 4th TREATMENT

BEFORE | AFTER 4th TREATMENT

COURTESY OF: CAROLYN JACOB, M.D.

COURTESY OF: BRIAN KINNEY, M.D.

COURTESY OF: ANITA STURNHAM, M.D.

COURTESY OF: SUNEEL CHILUKURI, M.D.
Body Sculpting with HIFEM technology (FAT AND MUSCLE)

BEFORE

AFTER 4th TREATMENT

COURTESY OF: ANITA STURNHAM, M.D.
First patient we treated, 3 treatments over 4 weeks
<table>
<thead>
<tr>
<th>Percentage</th>
<th>Effect Description</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>92%</td>
<td>Increase in FAT APOPTOSIS after 1 treatment</td>
<td>~4cm</td>
</tr>
<tr>
<td>16%</td>
<td>Increase in MUSCLE THICKNESS</td>
<td></td>
</tr>
<tr>
<td>19%</td>
<td>Reduction in ABDOMINAL FAT</td>
<td></td>
</tr>
<tr>
<td>11%</td>
<td>Reduction in DIASTASIS RECTI</td>
<td></td>
</tr>
<tr>
<td>11%</td>
<td>WAIST CIRCUMFERENCE reduction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VOLUMETRIC GROWTH of all three gluteal muscles</td>
<td></td>
</tr>
</tbody>
</table>
• The shape of buttocks is predominantly defined by gluteal muscles (g. Maximus, Medius and Minimus)
• By volume, gluteus maximus is one of the largest muscles in the human body

Large potential for firming and toning by HIFEM stimulation

BEFORE

3M POST-TREATMENT

Courtesy of Mariano Busso MD
EXAMPLE OF PATIENT RESULTS

BEFORE

AFTER Emsculpt

4 WEEKS AFTER 4th TREATMENT, COURTESY OF: ALAIN MICHON, M.D.
BeautyFill
First closed loop autologous fat transfer system

- System simultaneously combines:
  - Laser to assist in fat cell harvest
  - Aspiration to collect fat cells
  - Initial processing of fat cells to optimize viability
The Right Wavelength
1470nm laser through a conical tip

The Right Safety
Laser encased in cannula
Compared to traditional liposuction, the Beautyfill system resulted in:

- 38.9% more fat in a given collection volume
  - 40% of the volume collected in traditional ultrasound consists of oil and blood
  - Likely derived from damaged lipocytes
- Much higher consistency of lipocyte viability compared to mechanical liposuction
Baseline | Post 13 Weeks
---|---

Photos courtesy of J. Fathi, MD

<table>
<thead>
<tr>
<th>Fat Transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
</tr>
<tr>
<td>Procedure Time</td>
</tr>
<tr>
<td>Tx Cost</td>
</tr>
</tbody>
</table>

Baseline | After 6 Months
---|---

Photos courtesy of Y. Avellanet, MD

<table>
<thead>
<tr>
<th>Fat Transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
</tr>
<tr>
<td>Procedure Time</td>
</tr>
<tr>
<td>Tx Cost</td>
</tr>
</tbody>
</table>
Thank You!!!!!!  jillf5013@yahoo.com