Update on Fillers and Neuromodulators

Presented by Michael H. Gold, MD
Goldskin Care Center
Tennessee Clinical Research Center
Nashville, TN USA

Academic Appointments

• Assistant Clinical Professor
  Department of Medicine, Division of Dermatology, Nashville, TN USA
  Vanderbilt University School of Medicine: 2016 - 2014
  Vanderbilt University School of Nursing: 2006 - Present

• Adjunct Assistant Professor
  Meharry Medical College: 2013 - Present
  School of Medicine, Nashville, TN USA

• Visiting Professor of Dermatology
  Huashan Hospital, Fudan University (Shanghai Medical University), Shanghai, China:
  The First Affiliated Hospital of China Medical University, Shenyang, China: 2006 - Present
  Guangdong Provincial People’s Hospital, Guangzhou, China: 2013 - Present

• Visiting Professor of Plastic Surgery
  The First People’s Hospital of Foshan University, Guangdong, China: 2012 - Present
  The First Affiliated Hospital of Zhejiang University, Hangzhou, Zhejiang: 2013 - Present

Conflict of Interest

• Consultant to many pharmaceutical, cosmeceutical, laser and energy based device companies

• Consultant, performs research and speaks on behalf of numerous pharmaceutical and medical device companies

• For the benefit of this presentation, Consultant, Investigator, Speaker for Allergan, Merz, Galderma, Prolleenium, Suneva, Evolus, Revance, Neauvia, Crom, MTF, Alma, Clarisonic, Skinceuticals, Sente, SkinBetter Science, Revision, Altius, Topix, and Nutrafol
The Aesthetics Market is Booming

United States - International

Today, Only 7% of Aesthetics Considerers Worldwide Have Used Facial Injectables

Aesthetic Market Growth Catalysts

- Attitudes & perceptions are evolving
- Medical & surgical enhancements
- Digital & social media enable information flow
- More providers than ever before
Allergan Global Beauty Survey 2016-2017

Increasing Acceptability of Aesthetics

- 71% are excited about seeing a celebrity with a filled-in nasolabial fold
- 65% agree that aesthetic treatments have become more socially acceptable in the last 5 years
- 41% are unlikely to consider or try a skin care treatment

Millennial Aesthetics Users Have More Than Tripled in the U.S. in 5 Years

- More buying power than boomers
- They start earlier
- Prevention is on their mind

Digital & Social Media

- 50M Google searches on Medical Aesthetics
- 3.3M Picosure versus an Instagram right now
- Social Media Users
Fillers: What's Here and What's Ahead

**Abstract**
Soft tissue augmentation products (i.e., fillers) are used for the correction of appearance changes in aspects of the face, body, and hands. These off-label procedures are popular with both men and women. While some side effects do occur, New-Brand is supplied to the treatment of fine lines. Filler type and location are significant factors for success. To facilitate use, we present a review of results obtained by others and describe the clinical experience of our practice. 

**Keywords**
Dermal fillers; injectable; cosmetic; soft tissue augmentation

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**HA Dermal Fillers in Europe**

Number of HA dermal fillers in Europe is much superior to the US.

In France the Drug Agency ANSM published an updated list of Injectable dermal fillers declared in France July 31, 2012: > 90 (list available).

ANSM classified products as resorbable (3–6 months) slowly resorbable (6–24 months) non-resorbable.

The resorbable products mostly belong to HA- based products a duration of action between 3 -6 months

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**Fillers Available in Europe**

- Allohyal
- Aloe Vera
- Ac-hyal
- Belotero Basic®
- Belotero Soft®
- Captique
- CRM-Dermal Filler®
- Cryoform Touch
- DermaFill Deep
- MacDermol S and R®
- Macrolane®
- Matridur®
- Matridex®
- Perfectha®
- Prevelle®
- Prevelle Plus®
- Princess Touch®
- Princess Filler®
- Puragen™
- Puragen Plus
- Restylane Perlane®
- Restylane®
- Restylane SubQ®
- Restylane Touch®
- Restylane Vital®
- Restylane Vital light
- Restylane Lipp®
- ReDexis
- Reviderm Intra®
- Rodisan®
- Surgiderm® 18, 30
- Surgiderm® 24XP
- Surgiderm® 30XP
- Surgilips®
- Surgilift® Plus
- Teosyal Global action®
- Teosyal Deep Lines,
- Teosyal Ultra Deep
- Teosyal Kiss
- Teosyal Ultimate
- Teosyal Radience I
- Teosyal Radience II
- Varioderm®,
- Varioderm Plus
- Varioderm Subdermal
- Varioderm FineLine
- Visagel®
- Z-Filler
- Zetavisc L®
- Voluma Corneal®

No trials or any IB data needed for the CE-mark. YET!!
FDA Approved Indications

**Restylane® Refyne**
Correction of moderate to severe, facial wrinkles and folds (such as nasolabial folds) in patients over the age of 21
Injection into the mid to deep dermis

**Restylane® Defyne**
Correction of moderate to severe, deep facial wrinkles and folds (such as nasolabial folds) in patients over the age of 21
Injection into the mid to deep dermis
Restylane SkinBoosters

Not Available in the US

28

Treatment areas

Face, neck, decolletage and back of hands

Not Available in the US

29

Treatment results Restylane Vital™

Not Available in the US

30
Characteristics of Vycross Family of Products

<table>
<thead>
<tr>
<th>TABLE 1 Characteristics of Vycross Family of Products *</th>
<th></th>
</tr>
</thead>
</table>
| Indicator | Voluma 
Injection | Voluma 
Injection | Voluma 
Injection |
| Translucent | 164 mg/mL | 18 mg/mL | 17.6 mg/mL |
| Tolye | 13 mg/mL | 15 mg/mL | 14 mg/mL |
| Formulation | Smooth 1 top | Smooth 1 top | Smooth 1 top |
| Gel Diameter (mm) | 9.6 | 9.6 | 9.6 |
| Crosslinking | High | High | High |
| Duration | 12 months | 12 months | 12 months |
| Restore | 0% | 0% | 0% |
| Braille | 300 | 300 | 300 |
| Injectable | 300 | 300 | 300 |

*Not allmarkets/Innovations/Changes/Approvals/Uses
Belotero

The unique Cohesive Polydensified Matrix (CPM)

CPM® and Belotero® have been shown to be safe and effective.

The CPM® Technology is based on a distinct, double cross-linking process of the biodegradable hyaluronic acid gel with the unique "CTF®" core technology.

- Cross-linked proteins make it more stable in the tissues.
- Homogeneous distribution in the skin.

US Clinical Trials Expected to Begin in 2019.
US PIVOTAL STUDY

STUDY DESIGN

Qualified subjects had NLFs with 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 patient as well as adverse events recorded in a diary of each subject.

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.

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.
**PRIMARY EFFICACY ENDPOINT**

![Graph showing primary efficacy endpoint comparison between Revanesse®, Versa™, and Restylane®.]

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**

![Graph showing secondary efficacy variables comparison between Revanesse®, Versa™, and Restylane®.]

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**

![Graph showing the percentage of test patients reported swelling comparison between Revanesse® and Versa™.]

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.
VERSA BEFORE AND AFTER

1 Syringe of VERSA (1cc)
NLF: 0.9cc
Commissures: 0.1cc
Immediate Post treatment

VERSA BEFORE AND AFTER

3 Syringes (3cc) of VERSA
NLF: 1cc
Commissures: 0.2cc
Marionette lines: 1.4cc
Immediate Post treatment

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
Non-HA Fillers

Sculptra

Sculptra® – Biotech Industries/Dermik Aesthetics
- Polylactic acid hydrogel
- Sculptra® (injectable poly-L-lactic acid) is intended for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus

Product purchased in the US by Valeant Pharmaceuticals and sold to Galderma in 2014
For Volume, Duration, and Safety in patients with facial fat loss (lipoatrophy)

- **Volume**
  - Restores fullness of the face, creating a more natural appearance

- **Duration**
  - Improvements in dermal thickness persisted for up to 2 years

- **Safety**
  - Clinically proven safe and well tolerated. No skin test required. Biodegradable, biocompatible


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Sculptra®

Sculptra® Aesthetic received FDA clearance in July, 2009

For the correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles which are treated with the appropriate injection technique in healthy people.

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Before After

Photos courtesy of Michael H. Gold, M.D.
The Laser & Rejuvenation Center of Gold Skin Care Center, Nashville, TN
Sculptra Aesthetic

Before treatment | Immediately post treatment | 10 months post treatment

Photos courtesy of Michael H. Gold, M.D.
Gold Skin Care Center, Nashville, TN

Sculpta

Radiesse

Radiesse

Radiesse
US Regulatory Approvals

RADIESSE received approval from the FDA December 26, 2006 for facial soft tissue augmentation.
- Treatment of facial wrinkles and folds, such as nasolabial folds, marionette lines, etc.
- Correction of facial wasting as a result of HIV-associated Lipoatrophy

RADIESSE mixed with Lidocaine:
- FDA approved for facial aesthetic indication July 16, 2009

Merger of Merz and BioForm – end of 2009 = Merz Aesthetics

Treatment Results with Radiesse®
Moderate Nasolabial Folds

Untreated nasolabial folds
Nasolabial folds following treatment

*Final volume injected 0.6 mL
Injector: Dr. Humzah, UK
Treatment Results with Radiesse®
Nasolabial folds and lower cheeks

Untreated nasolabial folds and lower cheeks

Nasolabial folds and lower cheeks following treatment

* On average 1.1 mL/NGF are used to treat this area in most patients.

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CaHA for Hand Augmentation

Goldman 2015

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Mean Volume of CaHA injected, mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicenter, randomized, controlled, single-blind study of patients with both hands rated 2 or 3 on Merz Hand Grading Scale (MHGS)</td>
<td>Right hand: mean 2.6 mL (range 1.5-3.6)</td>
</tr>
<tr>
<td>Treatment group (n=170 hands) received CaHA mixed with 2% lidocaine HCl (27 G needle)</td>
<td>Left hand: mean 2.5 mL (range 1.4-3.6)</td>
</tr>
<tr>
<td>3-mo main study and follow-up of 12-mo post enrollment</td>
<td>Total: mean 5.1 mL (range 2.9-7.2)</td>
</tr>
</tbody>
</table>

Results: Safety

- AEs reported were generally expected, injection-related, and typical of other CaHA studies
- Mean duration of an AE was 6 days and nearly all AEs had initial onset < 4 days post treatment
- Bruising, swelling, redness, and pain were most frequently reported

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CaHA for Hand Augmentation (continued)

Goldman 2015 (continued)

Average Injection Volume
1-point Improvement in MHGS (51-year-old White female, Fitzpatrick Type III)

<table>
<thead>
<tr>
<th>Baseline Left Right</th>
<th>Injection Volume</th>
<th>Month 3 Left Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHGS 3 3</td>
<td>2.6 mL 2.6 mL</td>
<td>MHGS 2 2</td>
</tr>
<tr>
<td>Improvement</td>
<td>1 1</td>
<td>GAIS Improved</td>
</tr>
</tbody>
</table>
Treatment Results with Radiesse®
Hand Rejuvenation

Unreared back of the hand  Back of the hand following treatment

* On average 1.5 ml/ hand are used to treat this area in most patients.

Methodology and Consensus Objectives

Objective: Development of consensus-based guidelines for the usage of diluted and hyperdiluted CaHA for treating skin laxity and superficial wrinkles.

Focus: on neocollagenesis stimulating properties of diluted or hyperdiluted CaHA for the purposes of skin tightening, improvement of skin quality (defined as elasticity, firmness, roughness, superficial wrinkles and appearance).

A questionnaire served as a basis for the ensuing discussions.

Agreement of ≥75% of panel members constituted consensus.

Biostimulatory Concepts and Definitions of Diluted and Hyperdiluted CaHA

<table>
<thead>
<tr>
<th>Dilution Ratio</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1:1</td>
<td>Lower dilution provides volume and dermal remodeling</td>
</tr>
<tr>
<td>≥1:1</td>
<td>Higher dilution provides a biostimulation effect without volumization</td>
</tr>
<tr>
<td>1:1</td>
<td>Diluted CaHA</td>
</tr>
<tr>
<td>≥1:2</td>
<td>Hyperdiluted CaHA</td>
</tr>
</tbody>
</table>
Dilution Recommendations

Dilution with lidocaine and/or saline performed by physician (injector) immediately before use
Combined mixture tends to separate quickly
The higher the dilution, the faster the combined product separates

Sterile mixing environment
3-10 mL counter syringes; larger syringes for higher dilution
At least 20 passes between syringes to ensure product homogeneity
Bring back into original syringe

Recommended Treatment Paradigm

<table>
<thead>
<tr>
<th>Indication</th>
<th>mg Volume of lidocaine/saline</th>
<th>Dose Ratio</th>
<th>Injection Fees/Paradigm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parotid parotidectomy</td>
<td>1.5 mL/0.5 mL</td>
<td>1:1</td>
<td>Subdermal/Regrade (slow tanning)</td>
</tr>
<tr>
<td>Fascia</td>
<td>1.0 mL</td>
<td>1:2</td>
<td>Subdermal/Deep dermal/Regrade (slow tanning)</td>
</tr>
<tr>
<td>Dissection</td>
<td>0.5 mL</td>
<td>1:2</td>
<td>Immediate Subdermal/Regrade (slow tanning)</td>
</tr>
<tr>
<td>Mini-belly of the upper arm</td>
<td>2 mL/mL</td>
<td>1:2</td>
<td>Immediate Subdermal/Regrade (slow tanning)</td>
</tr>
<tr>
<td>Nodule</td>
<td>1.5 mL/0.5 mL cm²</td>
<td>1:1</td>
<td>Subdermal/Dermahasting/Inching</td>
</tr>
<tr>
<td>Nodules</td>
<td>1.0 mL/cm²</td>
<td>1:1</td>
<td>Subdermal/Dermahasting/Inching</td>
</tr>
</tbody>
</table>

*In select situations and in individuals with thinner skin, dilution ratios of 3:1 may be more appropriate

Volume Calculations in the Arms, Legs, and Abdomen

Formulation: 1.5 mL/100 cm² (area of 10x10 cm)

<table>
<thead>
<tr>
<th>Undiluted Dose</th>
<th>Dilution Ratio</th>
<th>Total Volume/cm² Injected</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 mL</td>
<td>1:1</td>
<td>3 mL</td>
</tr>
<tr>
<td>(one syringe)</td>
<td>1:2</td>
<td>4.5 mL</td>
</tr>
<tr>
<td></td>
<td>1:3</td>
<td>6 mL</td>
</tr>
<tr>
<td></td>
<td>1:4</td>
<td>7.5 mL</td>
</tr>
<tr>
<td></td>
<td>1:5</td>
<td>9 mL</td>
</tr>
</tbody>
</table>
Treatment of the décolletage in a 42-year-old woman before (A) and after (B) combination therapy with MFU-V and 1.5 mL CaHA diluted 1:2. Photograph B was taken 12 weeks after the third treatment of CaHA and 180 days after MFU-V.

To treat mild dermal irregularities in the buttocks, 1.5 mL CaHA was diluted with 3 mL of lidocaine and saline (1:2 ratio); 2 mL was injected per side in the deep dermis.

Skin tightening was accomplished by layering 1.5 mL CaHA diluted with 9 mL of lidocaine and saline (1:5 ratio) using a cross-hatching technique; 6 mL of solution was injected per side.

Figure demonstrates before and after three sessions using two syringes of CaHA.

Pre- and post-treatment images of a 32-year-old subject who developed acute deep striae rubrae in the anterior thigh after pregnancy.

Baseline appearance of striae (A) is much improved after treatment with 1:1 diluted CaHA followed by 3 sessions of topical ascorbic acid and microneedling (B) one month after the last treatment.

Images provided courtesy of Sabrina Fabi, MD.

Images reproduced with permission from Casabona G, Marchese P. Calcium hydroxylapatite combined with microneedling and ascorbic acid is effective for treating stretch marks. Plast Reconstr Surg Glob Open 2017;5:e1474.
• With limited evidence in the current literature, this report provides preliminary guidelines for the novel use of CaHA as a biostimulatory agent in the face and body
  • Future clinical trials will provide further evidence for optimal outcomes
  • CaHA has been used safely and effectively for over a decade to correct moderate-to-severe wrinkles and folds and soft-tissue volume loss
    • When injected more superficially in the subdermal plane in its diluted and hyperdiluted form, CaHA appears to promote dermal remodeling through stimulation of collagen and elastin for a skin-tightening effect and to improve superficial wrinkles, elasticity, and skin thickness.

**Conclusion**

BellaFill
What is BellaFill®

- Comprised of biocompatible PMMA microspheres suspended in a 'more rapidly' dissolving bovine collagen carrier with 0.3% lidocaine
- Created to induce "reactive" long-term collagen deposition
- 30-50 micron microspheres are too big to be phagocytized (20 microns is the cut off), but small enough to inject through a 26 gauge needle

Optimizing outcomes with polymethylmethacrylate fillers
J Cosmet Dermatol. 2018;1–7

BellaFill® - Nasolabial Folds

Before Treatment

5 weeks post treatment with 2cc

Photos courtesy of Michael H. Gold, M.D.
The Laser and Rejuvenation Center of Gold Skin Care Center, Nashville, TN
Results of Study Patient with Lasting Improvement

Bellafill® MOA Study Design

Single-center, open-label prospective study in 10 healthy female volunteers undergoing elective removal of abdominal skin

Bellafill® injected into upper and deep dermis. Areas marked to specify location of filler placement

8mm punch biopsies harvested and fixed in formalin at 1 week, 1-, 2-, 3- and 6 months

Paraffin-embedded tissue sections (5 μm) stained for Hematoxilin & Eosin, Colloidal Iron, Masson’s Trichrome, Collagen Types I and III and Elastin

Blinded histopathologic readings performed by Dermatopathologist.
• PMMA was observed to be smooth and even in appearance and persisted for the duration of the study
• Lymphocytes and macrophages infiltrated into the injected area as soon as 1 week post-injection
• Fibroblasts migrate into the filler and begin to produce extracellular matrix
• Inflammatory infiltrate persists for up to 6 months and continues to stimulate extracellular matrix production

Collagen Type III (200x)

• Collagen type III is expressed during embryonic development and early in the wound healing process
• Collagen type III begins to be evident as soon as 1 week following injection and fibers encapsulate the PMMA microspheres at 2 months and diminish at months 3 and 6

Collagen Type I (200x)

• Collagen type I is the most abundant protein found in skin
• Collagen type I is expressed later in the wound healing process, serving as a “mature” collagen
• Collagen type I was not found at 1 week following injection, but gradually increased over the course of the 6 month study and encapsulated individual PMMA microspheres present in the tissue
Collagen Type I Matures Over Time

5 Year Prospective BellaFill Safety Study

- The largest and longest prospective clinical study to date for dermal fillers in the US and EU

- Objectives
  - Overall assessment of Artefill safety in 1,000 subjects based upon the incidence of:
    - Anticipated & unanticipated adverse events (AEs)
    - Serious adverse events (SAEs)
    - The incidence of granuloma formation
    - Subjects’ assessment of satisfaction
  - Interim analysis was completed at 31 months

ASRS Responder Rates Over Time – 2 Point Improvement
Treatment of Atrophic Scarring
With PMMA-Collagen

Skin Surface with Acne Scars
Before PMMA-collagen

Skin Surface 6 Mo
After PMMA-collagen


Treatment of Facial Acne Scars with Microneedling Followed by Bellafill

Brian S. Berman, MD • Joel L. Cohen, MD
Barry E. Dibenedetto, MD • Jason J. Emer, MD
Roy G. Geronemus, MD • Michael H. Gold, MD
Gary Monheit, MD • Todd E. Schreiner, MD • Craig F. Teller, MD
Effectiveness – ASAS Scores

- MN + Bellafill® provided > 1.70 point improvement in ASAS vs. MN alone
- MN + Bellafill® treatment group continued to improve out to week 36, demonstrating response durability.

Effectiveness – PGAIS and SGAIS

- At week 24, MN + Bellafill® provided a clinically meaningful 26% point improvement vs. MN alone
- Response rate maintained at week 36

Representative Patient Images

- Baseline
- Week 12
- 3.5% HCA
- 3.5% HCA
Bellafill® Acne Scar Study Conclusions

In facial acne scars, microneedling followed by Bellafill® injection provided significantly more improvement in facial acne scars than microneedling alone.

Bellafill®-induced therapeutic benefits persisted for at least 6 months with no Bellafill®-related adverse events.

Bellafill® clinical safety summary

- Extensively Tested
- 1,142 patients treated with Bellafill across four U.S. clinical studies

- Low AE rates in studies
- Granuloma rate across all Bellafill® clinical studies was 1.2%

- Even lower AE rates in Market
- ~485,000 syringes distributed, Low AE rate 0.2%

Fillers Outside the US - 2018

and new US ones here and coming
Teosyal by Teoxane

Agreement with Strathprey Crown — Alphaeon
2018 — agreement over
Still unsure as to when Teosyal will be available in the US

Teosyal

The Princess® Injectables
HArmonyCa – Luminera’s innovative product, a breakthrough in the aesthetic world. It is based on a composite matrix of cross-linked Hyaluronic acid embedding Calcium Hydroxyapatite microspheres. HArmonyCa provides a strong, long lasting, volumizing and lifting effect.

HArmonyCa is designed to restore facial volume and correct facial deficiencies by promoting the generation of natural endogenous collagen.

Contains 1.25ml syringe X 2.

Composition:
- Calcium Hydroxyapatite (55.7%)
- Sodium Hyaluronate gel (20 mg/ml) cross-linked
- Phosphate buffer
ELLANSÉ™ presents a high efficacy, sustained volumizing capacity through collagen stimulation for natural results and long-lasting effects from 1 to 4 years. STAT Technology™ was developed to optimize the safety profile of ELLANSÉ™ Range.

Regenerate Beauty Through Collagen Stimulation

ELLANSÉ™
A new generation of collagen stimulators providing immediate correction followed by volumization through biostimulation with long-lasting effects from 1 to 4 years and high patient satisfaction.

Composition of ELLANSÉ™

ELLANSÉ™ has properties not seen in other similar soft tissue fillers. ELLANSÉ™ is composed of:
- 70% aqueous Carboxymethylcellulose (CMC) gel-carrier
- 30% synthetic Polycaprolactone (PCL) microspheres

This composition allows an immediate filling effect (CMC) followed by stimulation of the body's own collagen: neocollagenesis (PCL).
Composition of ELLANSÉ™

Immediate correction with CMC Gel:
- Aqueous gel-carrier
- GRAS Classified by FDA (“Generally Recognized As Safe”)
- CMC provides the filling capacity which creates volume after injection

Secondary and sustained biostimulation with PCL:
- Well-known biodegradable medical polymer
- Used in numerous CE and US FDA approved medical devices for over 20 years

PRODUCT PORTFOLIO
CL (CROSSLINKED) PRODUCTS

2 FAMILIES:
1. INTENSE (7 REFERENCES)
2. STIMULATE (2 REFERENCES)

NCL (NON CROSSLINKED) PRODUCTS
1. HYDRODELUXE (2 REFERENCES)

ALL PRODUCTS WITH HA FROM BACILLUS SUBTILIS
ALL PRODUCTS CROSSLINKED WITH PEG (EXCEPT HYDRODELUXE)
ALL PRODUCTS ARE SUPPLIED WITH A 1ml SYRINGE (EXCEPT HYDRODELUXE, WHICH IS 2x2,5ml)
ALL PRODUCTS CONTAIN GLYCINE AND L-PROLINE, WHY? COLLAGEN BOOSTER

PRODUCT RANGE

CL PRODUCTS CATEGORIES:
1. REGULAR FILLERS
2. GYNECOLOGICAL FILLER:
3. MEN'S LINE

PRODUCT LINE MAIN FEATURES
Biomaterial consisting of a purified agarose gel:

- CE marked and currently in an extended safety evaluation across 30 countries
- 100% Natural with no chemical cross-linking agents
- Agarose is a commonly used sugar/poly saccharide with safety shown in foods and multiple other applications
- Natural look and feel
- Safety profile demonstrated in the real world

Agarose is a natural polysaccharide

- Natural and sustainable source, no added chemicals or cross-linking agents
- Highly purified: it does not contain any protein and is free from bacteria.
- Free from toxicity from micro-organisms and free from impurities
- Agarose is safe, biocompatible to the human body, and fully biodegradable
- In clinical use, what you see is what you get
  - The result the patient leaves the treatment setting with is what they will see the next day
  - Does not pull water from surrounding tissues and swell

Histologic Study of Biocompatibility and Tissue Interactions between an Agarose Gel Filler and the Human Skin (Pirino & Mauliu, 6 months)

- In the hypodermis a good amount of filler is still present
- Newly formed collagenous bundles are clearly visible around the filler and in the context of the surrounding tissue.
- There is no capsule or granuloma formation (hematoxylin and eosin; original magnification X40).
- Well integrated into the existing, natural tissue
- Stimulated Fibroblasts
The Future of Fillers
Agarose (Algeness®)

Safety:
• Appears to dissipate quickly in blood vessels
• Potentially much less likely to cause occlusion than HA
• Theoretical reduced chance for sloughing and blindness
MTF Biologics: our core purpose

We save and heal lives
by honoring the donated gift, serving patients and advancing science

Growth Factors & Cytokines IN Adipose & Renuva

<table>
<thead>
<tr>
<th>Growth Factors/Cytokines</th>
<th>ADIPOSE</th>
<th>RENUVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDNF</td>
<td></td>
<td></td>
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<tr>
<td>IGF-1</td>
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<tr>
<td>VEGF</td>
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<tr>
<td>Lraptin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGF-5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Renuva contains factors relevant to neovascularization and adipogenesis

Pre-Clinical Testing – Athymic Mouse

H&E at 12 Weeks

- Subcutaneous injection
- Evaluation of adipogenesis (histology)
Mature AdipoCyes Present – Perilipin A Stain

ANIMAL STUDIES: ADIPOSE & BLOOD VESSEL FORMATION

Significant blood vessel formation observed at 12 weeks.

Dorsal Wrist Study – Safety & Viability in Humans

Drs. Sydney Coleman & Roger Khouri
15 patients
Single injection in dorsal wrist (2.5-5.5cc)
First in humans

Primary Objective: To assess Renuva safety, short term volume retention, local skin changes, subcutaneous fat changes over 16 weeks
Clinical Assessments: Systemic and local injection site assessment, photographic documentation,
Histological assessment: Adipogenesis (Perilipin), H&E
Outcome: Shown safe in first in human study
Kokai et al., PUBLISHED in PRS
Science + Clinical
Open Access (Feb 2019)

Primary Objective: To evaluate the remodeling of Renuva injected into subcutaneous tissues
Secondary Objectives: Assessment of rate of complications
Clinical Assessments: Systemic and local injection site assessment, adverse event diary, ultrasound, photographic documentation.
Histological assessment: adipogenesis, angiogenesis, collagen, elastin to evaluate local tissue reaction and remodeling of the extracellular matrix.

In-vivo Assessment in Abdominoplasty Patients
Dr Rubin (UPMC)
10 patients (5 at 12 weeks, 5 at 24 weeks)
6 injection sites per patient (20cc each)

• Demonstrated safety
• Capsule thinner, much less prominent
• Host infiltration
• Adipogenesis throughout
Adding histology analysis to examine endogenous cell infiltration into Renuva matrix during adipogenesis

Submission of manuscript to PRS by end of Q2
Semi-quantitative assessment: volume retention

<table>
<thead>
<tr>
<th>Fullness (0-4)</th>
<th>0 Pre</th>
<th>0 Post</th>
<th>1</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fullness</td>
<td>0</td>
<td>1</td>
<td>1.2</td>
<td>1.9</td>
<td>2</td>
<td>2.7</td>
<td>2.6</td>
<td>1.9</td>
<td></td>
</tr>
</tbody>
</table>

Renuva is safe and well-tolerated
- Low complications; zero at/after 4 weeks
- Achieve aesthetic correction; not over-correction
- Adipogenesis observed
- Volume retention up to 6 months
- Study to be submitted to ASJ by end of Q2

Renuva in Face study (ongoing)

A Multi-Phase, Prospective, Multi-Center, Single Blind, Clinical Study to Evaluate the Safety and Efficacy of Allograft Adipose Matrix (AAM) at Full- and Half Concentration for Pre-Jowl and Malar Augmentation to Correct Age-Related Volume Deficit in the Face
Protocol

3 sites: Drs. Michael Gold, Rod Rohrich, Steve Fagien
24 patients total

8 subjects per site

Half of subjects injected with diluted formulation (40%)

Up to 2cc (malar), 2cc (pre-jowl), re-injection option at 12 weeks up to 1cc each

6 month follow-up (blinded); long term follow-up (2 years)

Volume Change

<table>
<thead>
<tr>
<th>Subject 2-001</th>
<th>Right Cheek Total Volume Change</th>
<th>+1.70cc</th>
<th>Left Cheek Total Volume Change</th>
<th>+4.12cc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject 2-004</td>
<td>Right Cheek Total Volume Change</td>
<td>+3.30cc</td>
<td>Left Cheek Total Volume Change</td>
<td>+2.69cc</td>
</tr>
</tbody>
</table>

Baseline Pre-Treatment Visit to Baseline Post-Treatment Visit

Preliminary data subject to change
Clinical Summary

4 prospective clinical studies as of today

Renuva (adipose) formally studied in 59 subjects so far
Safe
Stimulate adipogenesis
Volume correction retained up to 6 months

HIV-Related Facial Lipodystrophy

Pre-Treatment

12 weeks Post-
Treatment

*4 cc Renuva per cheek

Mid-cheek
Parry-Romberg syndrome

Pre-Treatment

4 weeks Post-Treatment

Pre-Treatment

Post-Treatment

NasoLobial Fold

Pre-Treatment

12 weeks Post-Treatment
2 injections of 1.5cc Renuva per side 6 weeks apart

Tethered Scar

Pre-Treatment

8 weeks Post-Treatment
2cc Renuva
Renuva

What’s New On the Horizon For Toxins Coming To the Market
The PMFA J. Vol 6, Issue 3. February/March 2019, p. 23-4

Botulinumtoxin A

Gold Skin Care Center,
Tennessee Clinical Research Center
Nashville, TN USA.
Botulinum Toxin

Botulinum toxin injections have become the number one non-invasive cosmetic procedure in the world.

It has revolutionized cosmetic and aesthetic surgery.

It is safe and easy – or is it?

Millions and millions of injections worldwide.

Very low incidence of side effects.

But is it safe for everyone to inject?

Botulinum Toxin

Botulinum toxin injections are safe once you have mastered your facial anatomy.

Also once you realize that this is not cookie-cutter medicine – that each person is unique and different and that each person’s muscle configuration is unique and different.

But as more and more injectors are injecting botulinum toxin, and some have never practiced aesthetic medicine, the chance of adverse events certainly exists.
My Neighbor

One Way to Make Wrinkles Disappear

Ideal Characteristics of a Cosmetic Neuromodulator

- Rapid time of onset
- Long-term duration of action*
- Reversibility
- Toxin effect limited to muscles injected
- Definite yet controlled spread / field of effect
- Natural-appearing results
- Consistent results
- Minimal side effects
- Lack of immunogenicity

*In 2019, long-term duration of action seems to be a very big play
## Cosmetic Dermatology

**Toxins**

- **Botox Cosmetic** - Allergan
- Other toxins on or coming to the market:
  - Ipsen, Medicis (Valeant), now Galderma – Dysport,* Allergan
  - Mentor (Abbvie) – PurTox – 2014 Abbvie pulls PurTox
  - Merz – Neuronox,* BoCoulase
  - MedyTox (South Korea) – Neurotox
  - 2013 – MedyTox purchased by Allergan
  - Hugel (South Korea) – Botulinex
  - 2018 – Agreement with BoCoulase – studies to continue in US, Hugel to control US (?)
  - Chroma – a variety of toxins available from China
  - Lanzhou Biological Products Institute – real
  - Others – not real
- Relatox – 1st Russian Toxin - Thrall
- Evolus – Injevica

*2019 – Toxins Available in the US

## Cosmetic Neuromodulator Generic Names

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Common Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bottox Cosmetic</td>
<td>OnabotulinumtoxinA</td>
</tr>
<tr>
<td>Dysport</td>
<td>AbobotulinumtoxinA</td>
</tr>
<tr>
<td>Xeomin</td>
<td>IncobotulinumtoxinA</td>
</tr>
<tr>
<td>Revenance</td>
<td>DarabotulinumtoxinA</td>
</tr>
<tr>
<td>Evolus</td>
<td>PrabotulinumtoxinA</td>
</tr>
<tr>
<td>Croma (Hugel)</td>
<td>LetibotulinumtoxinA</td>
</tr>
</tbody>
</table>

Botox Cosmetic = Vistabel
Botulinum Toxin Type A
Botox and Botox Cosmetic - onabotulinumtoxinA

BOTOX is the Most Widely Studied and Well-Characterized Neurotoxin...

BOTOX® is the Most Widely Studied and Well-Characterized Neurotoxin...

Clinical Studies Overview
Before and After Treatment Photos

Phase 3 Study of OnabotulinumtoxinA Distributed Between Frontalis, Glabellar Complex, and Lateral Canthal Areas for Treatment of Upper Facial Lines
Dermatol Surg 2018;44:1437-1448

New Data 2018

Higher doses of Botox Cosmetic are well tolerated and offer better longevity than the traditional 20-unit dose, according to the results of a new clinical study.

Trials to evaluate the duration of effect and safety of Botox Cosmetic at 40, 60 and 80 unit doses versus the 20 unit dose in patients with moderate to severe glabellar lines.

The primary efficacy endpoint of ≥1 point improvement in Facial Wrinkle Scale (FWS) from baseline was met and was statistically significant for 40, 60 and 80 units versus 20 units in 226 subjects at 24 weeks.

Thirty-two percent of patients were responders at week 24 in the 40-unit group, 30.6 percent in the 60-unit group, and 38.5 percent in the 80-unit group as compared to 16 percent in the 20-unit group.
Higher doses of Botox Cosmetic are well tolerated and offer better longevity than the traditional with a ≥1 point improvement, the time to return to baseline also demonstrated a dose-effect. The median time on the Kaplan-Meier curve was 19.7 weeks for 20 units and 24.0 weeks for 40 units, suggesting the median benefit of 40 units is between 20 and 24 weeks.

The higher doses were safe and well tolerated. In a total 233 patients evaluable for safety, there was one serious adverse event unrelated to treatment. Overall treatment-related adverse events (AEs) compare favorably with USPI labeled AEs, and no new safety signals were identified. Across all studied doses there was one case eyelid ptosis at 80 units and one case eyebrow ptosis at 20 units.
BoNT/E1 Has 2 Unique Selling Propositions

BoNT/E1 Has 2 Unique Selling Propositions

- 65M/49% (considered the best
  non-invasive form of treatment)
- 1 of 4 (on-demand options available)

Dysport = Azzulare

Dysport:
Botulinum toxin A - abobotulinumtoxinA

Dysport available in Europe
- Ipsen
- Clinical trials support its effectiveness
- Different dilutions than Botox
- Galderma with marketing rights outside US – Azzulare

Dysport marketed in the US by Medicis
- FDA approved in April, 2009
- End of 2012 – Medicis bought by Valeant
Volume of reconstitution Study

A randomized, evaluator-blinded, comparative study to evaluate the efficacy and safety of different injection volumes of abobotulinumtoxinA in the glabellar lines

Aims of the Azzalure Volume Study

To evaluate how a two-fold increase in injection volume of Azzalure (abobotulinumtoxinA) may affect:

- Efficacy
- Safety
- Subject satisfaction

Comparing with labeled injection volume in treatment of glabellar lines
Same dose of Azzalure (abobotulinumtoxinA) for both injection volumes
Study Design and Objectives

**Study Design:**
Randomized, subject- and evaluator-blinded, comparative study using a parallel group design at two sites in Sweden.

**Study Objectives:**

**Efficacy was assessed by:**
- Evaluation of severity of glabellar lines using wrinkle severity rating scale (WSRS), a validated 5-point scale
- Compound muscle action potential (CMAP)

**Subject Satisfaction and Experience of onset of effect**

**Safety and injection pain**

---

Summary

- **125 sU/0.63 mL (EU label) => 0.05 mL/injection point**
- **125 sU/1.25 mL (2-fold dilution) => 0.10 mL/injection point**
  
  **Constant dose: 10 sU/point**
  
  Excellent efficacy with fast onset and long-lasting efficacy, and
  
  Similar safety profiles for both injection volumes
  
  Non-inferiority was demonstrated by the objective neurophysiological measurement of CMAP
  
  The larger volume does not cause more pain on injection

---

Subject Satisfaction for Two On-Label Injections

Volumes of Abobotulinum Toxin-A
Xeomin

Merz – Xeomin – N7201

Approved in Europe for blepharospasm and spasmodic torticollis
Smaller molecular size than other BTX-A
Comparative studies show that 1 U Botox is equivalent to 1 U Xeomin
Launched as BoCouture in Europe – EADV 2009
In the US for cosmetic indications as of August 2011
BTX-A Formulations For Medical Uses - Germany

BTX-A formulations with complexing proteins
approved for treatment of glabella lines in patients < 65 y (Germany)
well documented in other hyperfunctional facial lines e.g. crow's feet, horizontal forehead lines
high efficacy, safety and tolerability as assed in randomized, double-blind, controlled trials

Pure BTX-A neurotoxin formulation without complexing proteins
highly purified
free of immunogenic haemagglutinins
same efficacy and tolerability like BTX-A formulations with complexing proteins e.g. in patients
with focal dystonias and in healthy volunteers

Jost W et al 2005, Benecke et al 2004

---

Primary Outcome Measure
Composite Endpoint Treatment Success

![Graph showing treatment success]

---

Investigator: 1-Point Responders (Max Frown)

![Graph showing investigator-rated frown improvement]

---

CI=confidence interval; Diff RR=Difference in Response Rates (IncobotulinumtoxinA – placebo);
p-value calculated using Fisher’s Exact Test


Diff RR: 0.60; 95% CI [0.52, 0.68]  p<0.0001
BoCouture® = Xeomin® = IncobotulinumtoxinA Merz

Day 0 • Day 180

Photos courtesy of Michael H. Gold, M.D. Tennessee Clinical Research Center, Nashville, TN

XEOMIN & BOTOX: Equivalence for Glabellar Frown Lines

First randomized direct comparator study to date at FDA-recommended dose of 20 U for treatment of glabellar frown lines
Prospective, randomized, double-blinded, parallel-group study in 250 females (18-50 y), employing a single treatment with Xeomin or Botox, followed by 4 mo observation
Equivalence demonstrated at primary efficacy endpoint (1 mo)
Similar efficacy and tolerability profiles observed through 4 mo
Patient satisfaction ratings similar between groups
IncobotulinumtoxinA verse OnabotulinumtoxinA in the Treatment of Glabellar Facial Lines:

Evolus PrabotulinumtoxinA Manufactured by Daewoong Pharmaceuticals
Founded in 1948
PrabotulinumtoxinA approved in South Korea Nov 2013
Licensed for distribution in the US by Evolus, Inc.

Drug
Organism: C. botulinum type A
Complex: 900 kDa
Excipients: HSA (0.5mg), NaCl (0.9mg) per 100 U vial
Dwp-450 (Nabota®) Pivotal Korean Trial
Phase III Study: Result

Primary Endpoint
Non-inferiority at Week 4
Glabellar Line Severity 0 or 1 at Maximum Frown
by Investigator Assessment

Lower Limit of one-sided 97.5% CI: -1.53%

Secondary Endpoint
Glabellar Lines Severity at Maximum Frown
by Investigator Assessment

About Jeuveau™

Jeuveau™ 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

PLEASE SEE APPROVED USE AND IMPORTANT SAFETY INFORMATION INCLUDING BOXED WARNING ON PAGES 19-25

Nuceiva

PLEASE SEE APPROVED USE AND IMPORTANT SAFETY INFORMATION INCLUDING BOXED WARNING ON PAGES 19-25
U.S. Phase III Glabellar Line Studies

**Primary Endpoint Components**

- ≥2 Point GLS Improvement at Maximum Frown (Investigator and Subject Assessments)
- ≥2 Point Composite Score (Investigator and Subject agree)

**Day 30 Responder Rates**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Jeuveau™</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>EV001</td>
<td>77.5%</td>
<td>1.2%</td>
</tr>
<tr>
<td>EV002</td>
<td>82.5%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

**Day 120 Responder Rates**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Jeuveau™</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>EV001</td>
<td>4.6*</td>
<td>0</td>
</tr>
<tr>
<td>EV002</td>
<td>4.6*</td>
<td>0</td>
</tr>
</tbody>
</table>

- All p-values < 0.05
- Data on file, CSR EV-001, pg 5, 68
- Data on file, CSR EV-002, pg 5, 68

**Secondary Endpoints**

Head-To-Head Pivotal Phase III Data Versus Botox® Cosmetic

Primary Endpoint: Non-Inferiority at Week 4 (GLS at Max Frown)

- Difference between groups: 5.26%
- Lower limit of one-sided 97.5% CI: -1.53%
- Non-inferiority margin: -15%

Korea

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

EU/Canada

- The prabotulinumtoxinA formulation in this study is different than the Jeuveau™ formulation
- Data on file (CSR DWP450001, pg 78 & 55)
- Rzany et. al. “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” American Academy of Dermatology 2018 Late Breaker Session
Efficacy and Safety of PrabotulinumtoxinA for the Treatment of Glabellar Lines in Adults Subjects…

Dermatol Surg 2019;00:1-13

U.S.: Adverse Events
EU/CAN: Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>US PII EV-001</th>
<th>US PII EV-002</th>
<th>EU/CAN: PIII EV-033</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>32.1%</td>
<td>38.2%</td>
<td>32.7%</td>
</tr>
<tr>
<td>Related</td>
<td>13.3%</td>
<td>15.4%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Other AEs of Interest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planoce</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jeuveau™</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• Other AEs of Interest
  - Placebo (related)
  - EV-001: eyelid 0.6%, eyebrow 0.4%
  - EV-002: eyelid 1.2%, eyebrow 0.4%

Immunogenicity Testing
- Freeze Dried Formulation: Among 1,414 subjects treated with prabotulinumtoxinA, 2 subjects were found to have pre-existing antibodies and 2 subjects had treatment-emergent antibodies.
- Vacuum Dried Formulation (commercial formulation): No cases of seroconversion.

>2,100 Subjects Studied with No Drug Related Serious Adverse Events

Please see approved use and important safety information on pages 19-25.
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

Brett M. Fanning, MD, SHE, Shafi A. Ahmed, MD, BS, (Kevin) M. Liu, MD, Yonghee Kang, MD, Chia-Bin Su, MD, Mahood Yale, MD, James Haddad Carman, MD, August Caprio, MD, Kerry Donner, MD, Sari Farb, MD, Elie Fikrig, MD, MD, Adam H. Hoffer, MD, FRCSC, Peter Hovnanian, MD, Per Hustad, MD, Stuart Winer, MD, Michael N. Kaminer, MD, Howard Smith, MD, Michael Weisberg, MD, Frank H. Tosti, MD

Aesthetic Surgery Journal. April 1, 2019, online published

Study Design
- Multi-center, blinded, randomized, single dose study, 150 days
- N = 540, randomized 5:5:1 (Jeuveau™: Botox: 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)
**Jeuveau™ EU/CA Phase III Trial**

**Primary Endpoint**
Non-inferiority to Botox
A responder is a subject rated a 0 or 1 at Day 30 by Investigator Assessment using the 4 point GLS scale at maximum frown.

**Secondary Endpoints**
- GLS of 0 or 1 on D30 at max frown by SA
- ≥1 pt Subject Satisfaction Score on Day 30
- ≥1 pt GLS on Day 2 at max frown by IA
- ≥1 pt GLS D 150 at max frown by IA
- Δ to D 90, mean HADS Anxiety (HADS-A)
- Δ to D 90, mean HADS Depression (HADS-D)

**Source:** Data on file (CSR EVB-003, pg 5)
**Primary Endpoint**

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

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

Favors Jeuveau™

---

**Secondary Endpoints**

1. Improvement GLS at Maximum Frown
   - Investigator Assessment
   - Placebo: Day 2: 12.2%, Day 12: 57.0%
   - Botox: Day 2: 54.2%
   - Jeuveau™: Day 2: 10.6%

2. Subject Satisfaction
   - Investigator Assessment
   - Placebo: Day 150: 8.3%
   - Botox: Day 150: 34.4%
   - Jeuveau™: Day 150: 37.7%

---

**Exploratory Endpoint**

- Jeuveau™ vs Botox
- % Pt Improvement of GLS at Maximum Frown

---

Source: Data on file (CSR EVB-003, pg 5-6)
Cosmetic Dermatology

**Toxins**

Revance

DaxibotulinumtoxinA topical gel (RT001)
- Lateral Canthal lines – Phase III – endpoints not reached
- PROGRAM STOPPED

Hyperhidrosis – Phase II data – high efficacy at 4 weeks

DaxibotulinumtoxinA injectable (RT002)
- Phase II completed – safety, efficacy, and duration of 3 doses versus Botox and placebo – all primary endpoints met
- Phase III – clinical trials finishing

SAKURA 1 and 2 Phase 3 Pivotal Studies DaxibotulinumtoxinA for Injection (RT002)
for the Treatment of Moderate to Severe Glabellar Lines
Revance's Differentiated Neuromodulator

One THERAPEUTIC AGENT
- Patented Stabilizing Peptide DaxibotulinumtoxinA
- Positively charged peptide that binds with negatively charged area of molecule.
- NO animal-derived components or human albumin
- Highly purified, botulinum toxin type A molecule
- Unique EXCIPIENT
  + DaxibotulinumtoxinA for Injection (RT002)
  + DaxibotulinumtoxinA Topical Gel (RT001)

Two THERAPEUTIC MODALITIES
- In late-stage development
- Designed to be long lasting, injectable neuromodulator
- In preclinical development
- Designed to offer topical delivery of botulinum toxin

Current Focus
Potential for Better, Longer, Safer Treatment

DaxibotulinumtoxinA for Injection (RT002) is an investigational product

What is the Peptide?
The peptide excipient (RTP004) is a 35 AA cell penetrating peptide (CPP)

- Small: Molecular Weight of RTP004 is approximately 5kD
- Highly positively (+) charged amino acid sequence
  - Core of 15 consecutive lysines
  - Flanked at both ends by Protein Transduction Domains (PTDs)
- The peptide associates non-covalently and with high affinity to the (-) 150kD BoNT

Novel Stabilizing Peptide Excipient
- Small: Molecular Weight approximately 5 kD
- Highly positively (+) charged amino acid sequence
- Forms an electrostatic (noncovalent) interaction with 150kD neurotoxin
- Prevents adsorption of BoNT to container surfaces
- Prevents aggregation of BoNT
- Allows for formulation without HSA
BELMONT® Glabellar Lines Results Positive
DaxibotulinumtoxinA Demonstrates Long-Lasting Duration of Effect

6-month median duration of ≥1-point improvement as measured by IGA-FWS in the daxibotulinumtoxinA 40U dose, with 23.6 weeks vs. 18.8 weeks for onabotulinumtoxinA (p=0.030)

At 24 Weeks:
- DaxibotulinumtoxinA 40U and 60U doses continued to deliver clinically meaningful higher response rates vs. onabotulinumtoxinA as assessed by IGA-FWS and GAIS
- More specifically, daxibotulinumtoxinA 40U results indicate 31% of subjects maintain None or Mild wrinkle severity on IGA-FWS vs. onabotulinumtoxinA at 12%

Safety: DaxibotulinumtoxinA 40U appeared generally safe and well-tolerated with no ptosis

Next Steps: BELMONT results support selection of daxibotulinumtoxinA 40U dose to move forward into Phase 3 (SAKURA)

Injectable DaxibotulinumtoxinA for the Treatment of Glabellar Line
Dermatol Surg 2017;43:1321-1331

3 Open-Label Phase 3 Safety Study
SAKURA Phase 3 Clinical Development Program

- **SAKURA 1**: Open-label, 12-month study assessing the efficacy of single treatments (N = 406) in Canada.
- **SAKURA 2**: Open-label, 12-month study assessing the efficacy of single treatments (N = 238) in U.S.
- **SAKURA 3**: Open-label, long-term safety study across 3 GL cycles (N = 3830) in U.S.

In total over 2,000 patients received more than 6,200 DAXI 40U treatments across Phase 1 – 3 GL program.

SAKURA 3 Open-Label Safety (OLS) Study Design

- **SAKURA 3 Open-Label Safety Study**: A prospective, all-centre, open-label, repeat-dose study evaluating the safety and effectiveness of DaxibotulinumtoxinA for injection in 120 adult patients with glabellar lines across 108 sites in U.S. and Canada.

Treatment-Related Adverse Events (±21% in OLS)

<table>
<thead>
<tr>
<th>Event</th>
<th>SAKURA 3 OLS vs. SAKURA 1 and 2</th>
<th>Treatment Cycle 1 (%)</th>
<th>Treatment Cycle 2 (%)</th>
<th>Treatment Cycle 3 (%)</th>
<th>A2 Treatments (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>3.3%</td>
<td>3.0%</td>
<td>3.0%</td>
<td>3.0%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Upper eyelid edema</td>
<td>2.6%</td>
<td>1.3%</td>
<td>1.3%</td>
<td>1.3%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Lower eyelid edema</td>
<td>2.5%</td>
<td>1.3%</td>
<td>1.3%</td>
<td>1.3%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Sympathetic pain*</td>
<td>0.9%</td>
<td>0.9%</td>
<td>0.9%</td>
<td>0.9%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

* Subjects were followed for up to 3 years after randomisation to anti-wrinkle botulinum toxin A (A2) treatment.
None or Mild Responder Rate by IGA-FWS over Time

SAKURA 3: OLS Alongside SAKURA 1 and 2
SAKURA 1, 2, and 3 Study Outcomes for None or Mild Response on IGA-FWS Consistent Between Studies and Treatment Cycles

Proportion of Subjects Who Achieve ≥2 Point Composite Response at Max Frown at Week 4 in SAKURA 1, 2, and 3

Two-Point Composite Response Comparable Across SAKURA Studies and Treatment Cycles

Time to Loss of None or Mild Wrinkle Severity on Both IGA-FWS and PFWS

SAKURA 3: OLS Alongside SAKURA 1 and 2
Median Duration of 24 Weeks in SAKURA 3 Treatment Cycles 1 and 2 Consistent with Time to Loss of None or Mild Observed in SAKURA 1 and 2
Time to Return to Baseline Wrinkle Severity on Both IGA-FWS and PFWS

Sakura 3 OLS Alongside Sakura 1 and 2
Median Duration of 28 Weeks Achieved in Sakura 3 Treatment Cycles 1 and 2 Consistent with Time to Return to Baseline Observed in Sakura 1 and 2.

Median (95% CI)

OLS Treatment 1 (n=2380)
28.0 (28.0, 28.1) weeks

OLS Treatment 2 (n=882)
28.1 (28.0, 28.4) weeks

Sakura 1 (n=201)
27.7 (24.7, 28.0) weeks

Sakura 2 (n=204)
26.0 (24.1, 28.0) weeks

Female - Example 2 – Point Improvement by IGA – FWS & PFWS at Week 4

Example 2-Point Improvement by IGA-FWS & PFWS at Week 4
Two Point Quantified Duration of Effect Through Week 16 and 1 Point Improvement Quantified Through Week 32 in 23-year-old Female.

Female - Example 2 – Point Improvement by IGA – FWS & PFWS at Week 4
Cosmetic Dermatology

Toxins
Hugel – makers of one of the new toxins - Botulax

US Clinical Trials wrapping up in US with Croma from Austria
Many names around the world for this toxin
Regenox
Zentox
Reage
Magnion
Hugel Toxin
Juvenlife

Global Approval

Asia:
Korea (100, 20, 200, 150 U), Thailand (50, 100, 200 U), Philippines (100 U), India (100 U), Vietnam (100 U), China (Phase II), Taiwan, Kuwait (100 U), Mongolia (100 U)

Europe:
Ukraine (50, 100 U), Azerbaijan (100 U), Georgia (50, 100 U), EU (Phase III), Russia (50, 100 U)

Central & Latin America:
Peru (100 U), Uruguay (100 U), Paraguay (100 U), Bolivia (50, 100, 200 U), Chile (50, 100, 200 U), Columbia (50, 100, 200 U), Ecuador (50, 100 U), Honduras (50, 100, 200 U), El Salvador (100 U), Costa Rica (50, 100, 200 U), Guatemala (100 U), Panama (100 U), Dominican Republic (50 U), Brazil (50, 100, 200 U), Costa Rica (50, 100, 200 U)

North America:
US/Canada (Phase III)
For more information regarding these clinical studies, please visit: https://www.clinicaltrials.gov/
Outcome Measures

Primary Outcome Measures:
1. Facial Wrinkle Scale (FWS) score of 0 or 1 and an improvement of ≥ 2 points in FWS score (at maximum frown) at week 4 visit relative to baseline, based on both the investigators' and the subjects' in-clinic assessments.
   [Time Frame: week 4 relative to baseline]

INN: letibotulinumtoxinA

Secondary Outcome Measures:
1. Percentage of responders at maximum frown at week 12 [Time Frame: week 12]
2. Percentage of responders at week 16 [Time Frame: week 16]
3. The proportion of subjects with a ≥ 1 point reduction in FWS score at rest at week 4 based separately on the investigators' and the subjects' in-clinic assessments [Time Frame: week 4]
4. Percentage of responders at week 20 or later [Time Frame: week 20]
5. Frequency, severity and causal relationship of AEs, SEAs and AESIs [Time Frame: throughout study completion (60 weeks)]

INN: botulinumtoxinA

New Toxins Coming to the Market

• Several new toxins primed to make an entrance into the marketplace
• These may change the landscape
• These may be do nothing new
• These need to be "real" toxins and not "fake" as there are still plenty of fake toxins out there