Update on Fillers and Neuromodulators

New Frontiers in Cosmetic Medicine Symposium
November 16 – 17, 2019
Hasbrouck Heights, NJ
Academic Appointments

- Assistant Clinical Professor
  - Department of Medicine, Division of Dermatology, Nashville, TN USA
    - Vanderbilt University School of Medicine: 2006 - 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: 2006 - Present
  - The First Hospital of China Medical University, Shenyang, China: 2008 - Present
  - Guangdong Provincial People’s Hospital, Guangzhou, China: 2013 - Present

- Visiting Professor of Plastic Surgery
  - First People’s Hospital of Foshan University, Guangdong, China: 2012 - Present
  - The First Affiliated Hospital of Zhejiang University, Hangzhou, Zhejiang: 2013 - Present
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, Prolenium, Suneva, Evolus, Revance, Neauvia, Croma, 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

United States

159M
Women and Men Age 18 to 75 with Target Household Income

65M
Would Consider Facial Injectables

4M
Treated with Facial Injectables

6% Penetration

International

375M
Women and Men Age 18 to 65 with Target Household Income

153M
Would Consider Facial Injectables

11M
Treated with Facial Injectables

7% Penetration


1. Includes Canada, Eu, Australia, China, Brazil, Russia, Turkey and Saudi Arabia.

2. Consists of 15% weighted average of men and women based on two online surveys. 1) Allergan 2016 Global Beauty Trends survey with 1,700 women ages 18-65 in 14 countries.

2) BCG 2017 US medical aesthetics survey with 1,436 women and 298 men age 18-75.
Aesthetic Market Growth Catalysts

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

Increasing Acceptability of Aesthetics

- 71% are worried about wrinkles or other facial features
- 65% agree that aesthetics treatments have become more socially acceptable than 5 years ago
- 41% are seriously considering a facial injectable to enhance, change or treat the face

Interviewed Online 7,700 Women 18–65 Years-Old in 16 Countries
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

Source: 2014-2018 Allergan Sales Analysis and Billboard Distinctors Data Base
American Global Beauty Survey 2016, 2017

Millennial Growth
Over 1M
Millennial Facial Injectable Users expected in 2018

2014 2015 2016 2017 2018
0.29 0.38 0.56 0.74 1.01
Digital & Social Media: Enabling Information Flow

50M Google Searches on Medical Aesthetics*

3.3M #botox posts on Instagram right now**

Social Media Users

- Facebook: 2B (1.3B)
- Instagram: 1B
- Twitter: 200M
- Snapchat: 178M

*Google AdWords Research & Allergan Data, 2018
**Social Instagram
Provider Expansion 2012-2017

40% Increase in Providers Globally from 2012–2017 Is Improving Access

Source: Allergan ship-to accounts data for U.S. and International 2012-2017
Facial Injectable Market Projected to Double by 2025

Globally penetration is at 7% and expected to reach 13% by 2025.
Global Millennial & Gen X Movements

Millennials expected to triple while Gen X almost doubles by 2025

<table>
<thead>
<tr>
<th></th>
<th>2017</th>
<th>2025</th>
</tr>
</thead>
<tbody>
<tr>
<td>Millennials</td>
<td>6%</td>
<td>16%</td>
</tr>
<tr>
<td>Gen X</td>
<td>7%</td>
<td>13%</td>
</tr>
<tr>
<td>Boomers</td>
<td>8%</td>
<td>10%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>7%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Penetration Rate

Aegon in Britain, the UK & Ireland subsidiary of Aegon N.V. for data analysis.
Fillers: What’s Here and What’s Ahead

Fillers: What’s Here and What’s Ahead
Nowell Solish, MD, FRCP(C)*

- **Abstract**
  Soft tissue augmentation products (or fillers) are used for the correction of age-related changes in areas of the face. The most common filler material is hyaluronic acid, which is synthetically cross-linked. These materials are generally safe, but some side effects do occur. New fillers are expected to be approved in the United States in the near future.
  © 2016 published by Frontline Medical Communications

- **Keywords**
  Delayed nodules; fillers; hyaluronic acid; NASHA; soft tissue augmentation
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
Fillers Available in Europe

- Ac-Hyal®
- Alyna
- Belotero Intense®
- Belotero Basic®
- Belotero Soft®
- Captique
- CRM-Dermal Filler®
- Emervel Touch
- Emervel Classic
- Emervel Deep
- Emervel Lip
- Emervel Volume
- Esthelis Soft
- Esthelis Basic,
- Fortéliis Extra
- Modelis
- Hyacell®
- Hyacorp S
- Hyacorp L
- Hyal 2000 Injectio
- Hyal-System®
- Hyaluderm®
- H. Revitalize
- Hydrafill Grade 1, 2, 3®
- Hydrafill Softline®
- Hydrafill Softline MAX®
- Hylaform Fine Lines®
- Hylaform®
- Hylaform Plus®
- Isogel 1, 2, 3
- Juvederm ultra® 2
- Juvederm ultra 3
- Juvederm ultra 4
- Juvederm ultra smile
- Juvederm Voluma
- Juvélift Corneal®
- Mac Dermol S and R®
- Macrolane®
- Matridur®
- Matridex®
- Perfectha®
- Prevelle®
- Prevelle Plus
- Princess Touch
- Princess Filler
- Princess Volume
- Puragen™
- Puragen Plus
- Restylane Perlane®
- Restylane®
- Restylane SubQ®
- Restylane Touch®
- Restylane Vital®
- Restylane Vital light
- Restylane Lipp®
- Restylane Macrolane
- Revanesse
- Revanesse Ultra
- ReDexis
- Reviderm Intra®
- Rofilan®
- 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
- Viscontour®
- Visagel®
- Z-Filler
- Zetavisc L®
- Voluma Corneal®

No trials or any EB 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® instructions for Use for full prescribing and safety information.
Injection System
Restylane Vital

Not Available in the US
Restylane SkinBoosters

Not Available in the US
Treatment areas

Face, neck, decolletage and back of hands

Not Available in the US
### TABLE 1 Characteristics of Vycross Family of Products

<table>
<thead>
<tr>
<th></th>
<th>Volbella*</th>
<th>Vollift*</th>
<th>Voluma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Lips</td>
<td>Nasolabial folds</td>
<td>Cheek and chin area</td>
</tr>
<tr>
<td>Implantation depth</td>
<td>Lip mucosa</td>
<td>Deep dermis</td>
<td>Deep dermis</td>
</tr>
<tr>
<td>Total HA concentration</td>
<td>15 mg/mL</td>
<td>17.5 mg/mL</td>
<td>20 mg/mL</td>
</tr>
<tr>
<td>Formulation</td>
<td>Smooth viscous gel</td>
<td>Smooth viscous gel</td>
<td>Smooth viscous gel</td>
</tr>
<tr>
<td>Gel hardness/viscosity $(G' @ 5 \text{ Hz})$</td>
<td>271 Pa</td>
<td>340 Pa</td>
<td>398 Pa</td>
</tr>
<tr>
<td>Cohesivity</td>
<td>19 gmf</td>
<td>30 gmf</td>
<td>40 gmf</td>
</tr>
<tr>
<td>Duration</td>
<td>Up to 12 months</td>
<td>Up to 12 months</td>
<td>Up to 24 months</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>0.3%</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Needle gauge and length</td>
<td>30G ½ in</td>
<td>30G ½ in</td>
<td>27G ½ in</td>
</tr>
<tr>
<td>Shelf life</td>
<td>2 years</td>
<td>2 years</td>
<td>2 years</td>
</tr>
</tbody>
</table>

*Not yet approved by US Food and Drug Administration. *$^1$Approximate values.
Belotero
The unique Cohesive Polydensified Matrix (CPM®)

CPM® sets Belotero® apart from conventional hyaluronic acid fillers.

*Conventional filler: Biphasic gel*
The biphasic gel showed many fragments and a non-cohesive matrix.

*Belotero®: Monophasic gel with CPM®*
In contrast, Belotero® resulted in a highly stable, cohesive matrix.

The CPM® Technology is based on a dynamic, double cross-linking process of the cohesive monophasic hyaluronic acid gel with the stabilizer BDDE.

- Low viscosity properties make it able to fill in even the tightest intradermal spaces
- Homogenous distribution into the dermis

The unique stable matrix creates **long lasting results.**
Modelis = Belotero Volume

US Clinical Trials Expected to Begin in 20__??
Revanesse® by Prollenium

2017 – US FDA Approval of Versa
The Revanesse® Family of Products

The Revanesse® family of products incorporates the latest advancements in cross-linking technology, resulting in a high quality, safe, long lasting dermal filler. The Revanesse® family of products utilize the highest concentration of stabilized hyaluronic acid (HA) available in addition to the rejuvenating properties of non cross-linked HA. This line of products includes:

Versa = Ultra
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
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
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

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.
Non-HA Fillers
NewFill/ 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

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.
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*
## CaHA for Hand Augmentation

### Goldman 2015<sup>1,2</sup>

<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 2.6 mL (range 1.4-3.6)</td>
</tr>
<tr>
<td>• 3-mo main study&lt;sup&gt;1&lt;/sup&gt; and follow-up of 12 mo postenrollment&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Total: mean 5.1 mL (range 2.9-7.2)</td>
</tr>
<tr>
<td>• Primary effectiveness: percentage of patients achieving ≥1-point improvement on MHGS at 3 mo</td>
<td></td>
</tr>
<tr>
<td>• Secondary effectiveness: change from baseline at month 3 on MHGS (blinded evaluator) and GAIS (subject assessment)</td>
<td></td>
</tr>
<tr>
<td>• Safety assessed by recording AEs observed during study and real-time hand function tests</td>
<td></td>
</tr>
<tr>
<td>• 78 subjects (69%) received retreatment at 6 mo</td>
<td></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 6.6 days and nearly all (88.5%) had initial onset ≤14 d post-treatment
- Bruising, swelling, redness, and pain were most frequently reported
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></th>
<th>Baseline Left</th>
<th>Baseline Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHGS</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Injection Volume</td>
<td>2.6 mL</td>
<td>2.6 mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Month 3 Left</th>
<th>Month 3 Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHGS</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>MHGS Improvement</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>GAIS</td>
<td>Improved</td>
<td></td>
</tr>
</tbody>
</table>
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 neocollagensesis 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.
<table>
<thead>
<tr>
<th>Description</th>
<th>Dilution Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower dilution provides volume and dermal remodeling</td>
<td>&lt;1:1</td>
</tr>
<tr>
<td>Higher dilution provides a biostimulation effect without volumization</td>
<td>≥1:1</td>
</tr>
<tr>
<td>Diluted CaHA</td>
<td>1:1</td>
</tr>
<tr>
<td>Hyperdiluted CaHA</td>
<td>≥1:2</td>
</tr>
</tbody>
</table>

Biostimulatory Concepts and Definitions of Diluted and Hyperdiluted CaHA
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 syringe; 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>Avg Volume of Undiluted Radiesse</th>
<th>Dilution Ratio</th>
<th>Injection Plane/Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan-facial rejuvenation</td>
<td>1.5 mL/side</td>
<td>Most commonly 1:1; up to 1:3</td>
<td>Subdermal/Retrograde linear fanning</td>
</tr>
<tr>
<td>Neck</td>
<td>1.5 mL</td>
<td>1:2 to 1:4</td>
<td>Immediate subdermal/Retrograde linear threads</td>
</tr>
<tr>
<td>Décolletage</td>
<td>1.5 mL</td>
<td>1:2 to 1:4†</td>
<td>Immediate subdermal/Retrograde linear threads</td>
</tr>
<tr>
<td>Mild laxity of the upper arm</td>
<td>3 mL/arm</td>
<td>1:2†</td>
<td>Immediate subdermal/Retrograde linear fanning</td>
</tr>
<tr>
<td>Abdomen</td>
<td>1.5 mL/100 cm²</td>
<td>1:1</td>
<td>Subdermal/Crosshatching or fanning</td>
</tr>
<tr>
<td>Buttocks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gluteal sagging; mild dermal irregularities</td>
<td>1.5 mL per side</td>
<td>1:2 and 1:6, layered</td>
<td>Deep dermal/Crosshatching</td>
</tr>
<tr>
<td>Mild laxity of the legs</td>
<td>1.5 mL/100 cm²</td>
<td>1:2†</td>
<td>Immediate subdermal/Horizontal &quot;rasping&quot;</td>
</tr>
<tr>
<td>Cellulite</td>
<td>1.5 mL per side</td>
<td>1:1</td>
<td>Subdermal/Vectored fanning</td>
</tr>
<tr>
<td>Striae</td>
<td>1.5-3 mL per session</td>
<td>1:1</td>
<td>Subcutaneous to superficial dermis/Microbolus or retrograde linear thread</td>
</tr>
</tbody>
</table>

†In select situations and in individuals with thicker skin, dilution ratios of 1:1 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 Radiesse</th>
<th>Dilution Ratio</th>
<th>Total Volume/100 cm² Injected</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 mL (one syringe)</td>
<td>1:1</td>
<td>3 mL</td>
</tr>
<tr>
<td></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>
Conclusion

• 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.
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

Michael H Gold MD1,2 | Neil S Sadick MD2,3

1Gold Skin Care Center, Nashville, TN, USA
2Sadick Dermatology, New York, NY, USA
Correspondence
Michael H Gold, Gold Skin Care Center, Nashville, TN, USA.
Email: dgold@goldskincare.com

Summary
Introduction: The ideal filler should be long-lasting, biocompatible, chemically inert, soft and easy to use, and have a long history of safety. This review focuses on the evolution and development of the PMMA-collagen gel, Bellafill, and the 10 years of postmarketing experience of Bellafill since it received premarket approval (PMA) from the FDA as Artefill in 2006. Artefill was rebranded to Bellafill in 2015.
Methods: The authors conducted a literature search on PubMed for key articles describing the steps in which Arteplast, a PMMA filler developed in 1989, led to the development of Bellafill, the only PMMA filler approved by the US FDA for the treatment of nasolabial folds and acne scar correction. The factors governing efficacy and safety were also evaluated for the major PMMA fillers available in the world.
Results: The process of manufacturing and purifying PMMA has played a major role in minimizing adverse events for Bellafill. Postmarketing surveillance data for the 2007-2016 period show that for more than 300,000 Bellafill syringes distributed worldwide, 11 confirmed granulomas (excluding clinical trial data) (0.002% of syringes sold) have been reported. Data on other PMMA fillers are limited and inconsistent. The authors suggest that adverse events are often attributable to lack of proficiency in treatment technique and other factors.
Conclusion: Bellafill has demonstrated an excellent safety and effectiveness profile in multiple clinical studies, customer feedback, and 10 years of postmarketing surveillance experience. Adverse events occur with all fillers for a variety of reasons. In addition to quality of the product, injector skill and technique are critical to ensuring good clinical outcomes.
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 areas 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 diminishes at months 3 and 6.
• 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

1 month

6 months
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

Blinded through 6 months

Responder = ≥ 2-point improvement in ≥ 50% of treated scars

Treatment of Facial Acne Scars with Microneedling Followed by Bellafill®

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

- MN + Bellafill® provided > 0.70 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

At week 24, MN + Bellafill® provided a clinically meaningful 40% point improvement vs. MN alone
Response rate maintained at week 36
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

1,542 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

~685,000 syringes distributed, Low AE rate .12%
Fillers Outside the US - 2018

and new US ones here and coming
Teosyal by Teoxane

Agreement with Strathprey
Crown – Alphaseon
2018 – agreement over
Still Unsure as to When Teosyal will be available in the US
Teosyal
The Princess® Injectables

Mesotherapy
Universal
Deep & Volumetric

Universal Lidocaine
Deep & Volumetric Lidocaine
Saypha
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™ Product Presentation
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.
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 bioresorbable medical polymer
- Used in numerous CE and US FDA approved medical devices for over 20 years
Neauvia

PRODUCT PORTFOLIO
CL (CROSSLINKED) PRODUCTS

2 FAMILIES:
- INTENSE (7 REFERENCES)
- STIMULATE (2 REFERENCES)

NCL (NON CROSSLINKED) PRODUCTS
- HYDRODELUXE (2 REFERENCES)

CL PRODUCTS CATEGORIES:
1. REGULAR FILLERS
2. GYNECOLOGICAL FILLER:
3. MEN’S LINE
PRODUCT LINE MAIN FEATURES

- 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
MTF = Musculoskeletal Transplant Foundation
Founded in 1987
501(c)3 Non Profit Tissue Bank
  Procure, process and distribute donated human tissue
  Deceased and living donors
Founded by Orthopedic Surgeons
  High quality, safe source of allografts
  Not-for-profit foundation
  Advance the science of tissue transplantation
Governed and Guided by Surgeons Today
MTF Biologics: fast facts

More than 8.5 Million allografts distributed
More than 130,000 tissue donors processed
Zero viral disease transmission in our 30 year history
More than 100 peer-reviewed publications
64 issued and 19 pending US patents
More than $55 Million in research funding

Every minute of every day, an MTF Biologics allograft is used to save or heal a life
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

Growth Factors/Cytokines

Substances that stimulates/regulates cell processes (proliferation, growth, differentiation)

<table>
<thead>
<tr>
<th>Factor</th>
<th>ADIPOSE</th>
<th>RENUVA</th>
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<tbody>
<tr>
<td>Angiopoietin-2</td>
<td>✔️</td>
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<tr>
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<tr>
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<td>IGF -1</td>
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<tr>
<td>IL -6</td>
<td>✔️</td>
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<tr>
<td>Key adipogenic factors</td>
<td></td>
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</tbody>
</table>

Renuva contains factors relevant to neovascularization and adipogenesis
Pre-Clinical Testing – Athymic Mouse

- Subcutaneous injection
- Evaluation of adipogenesis (histology)

H&E at 12 Weeks
Mature AdipoCyttes Present – PerilipIn A Stain
Significant blood vessel formation observed at 12 weeks.

Adipocyte morphology apparent at 12 weeks.
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
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.
Demonstrated safety
Capsule fairly prominent
Host infiltration
Adipogenesis outer perimeter

Progressive adipogenesis (Perilipin A staining)

- 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
10 Patients, 4 Sites (Drs. Gold, Kinney, Kaminer, Rohrich)

Option for re-injection of the site is included in the protocol

**Primary Objective:** Evaluate retention of Renuva over 24 weeks following injection in patients with bilateral atrophic temples

**Secondary Objectives:** Evaluate well being/adverse events over 24 weeks following injection; histological evaluation of injection site via biopsy at 8 Weeks

---

Temple Study (volume retention with time)

Pockets of adipose formation
Semi-quantitative assessment: volume retention

**FULLNESS - NORMALIZED TO BASELINE**

- **Weeks:** 0 Pre, 0 Post, 1, 4, 8, 12, 16, 20, 24
- **Fullness (0-4):**
  - Baseline correction
  - Values: 0, 0, 2.8, 1.2, 1.9, 1, 2, 2.7, 2.6, 1.9

The graph shows the normalized fullness over time, indicating changes from baseline.
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
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

Renuva in Face study (ongoing)
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)
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
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

What’s new on the horizon for toxins coming to the market?

BY MICHAEL H. GOLD

With the ever increasing demand for injectable treatments, it is important to keep abreast of new developments in the field. International expert Michael Gold reviews the new toxins due to be hitting the market in the next year.

We are very fortunate in cosmetic and aesthetic dermatology that we have an array of minimally invasive cosmetic treatments that have grown in prominence and numbers over the past five years. According to the American Society of Dermatologic Surgery Survey Dermatologic Procedures performed in 2017 [1], dermatologists performed nearly 5 million procedures in the United States in 2017, up from 4.6 million procedures in 2012. The survey found that nearly 2.7 million procedures were done with injectables consisting of neuromodulators and soft tissue filling agents, with an increase of some 71% over the past six years. A third of these injectable treatments occurred in the 40-59 year age group. That latter market was primarily seeking Miladynum, a new drug for cosmetic dermal tightening. In the US, ZO Laboratories received FDA approval for its product, Q-Med, for cosmetic dermal tightening. We can see the benefits of these injectables in the clinical setting, and I believe that these will be very useful to our patients.

The third US toxin is Xeomin, which received its FDA approval in July 2015. It is the best way to utilise these toxins to make them work best for your patients. So, with these available toxins in the US market, the logical question thus arises, do we need any more toxins for us to choose from for our patients? Again, this is a question which is beyond the scope of this manuscript but a question nonetheless to consider as we are poised, at least in the US, to have at least three more toxins coming to the market over the next several years. What advantages might they have, if any? The question needs to be answered and for us, as clinicians, we need to factor into how and why we use a particular toxin. One thing that the current toxins have in their favor is the boosts programmes that have been put into place by the companies. Their amount of reporting or companies is not enough. These dates will soon tell. However, the recent approval of Xeomin, an alternative to Botox, is a significant event in the field of aesthetic medicine.
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 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.
THE MANY FACES OF THE BOTOX BABE...

HAPPY
SAD
WORRIED
EXCITED
DEPRESSED
ASLEEP

© 2002 HANDELSMAN—NEWSI
2013 -- Botoxicons

Emoticons

Botoxicons

whyatt.com.au
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
Toxins

**Botox Cosmetic*** - Allergan

Other toxins on or coming to the market -
- Ipsen, Medicis (Valeant), now Galderma – Dysport, * Azzulare
- Merz – Xeomin, * BoCouture
- MedyTox (South Korea) – Neuronox
  - 2013 – MedyTox purchased by Allergan
- Hugel (South Korea) – Botulax
  - 2014 – marketing agreement with Chroma
  - 2018 – Agreement with Bain – studies to continue in US, Hugel to control US (?)
- ChinaTox – a variety of toxins available from China
  - Lanzhou Biological Products Institute – real
  - Others – not real
- Relatox – 1st Russian Toxin - ?real
- Evolus – Jeauvea

*2019 – Toxins Available in the US
Cosmetic Neuromodulator Generic Names

- Botox Cosmetic -- *onabotulinumtoxinA*
- Dysport -- *abobotulinumtoxinA*
- Xeomin -- *incobotulinumtoxinA*
- Revance -- *daxibotulinumtoxinA*
- Evolus - *prabotulinumtoxinA*
- Croma (Hugel) -- *letibotulinumtoxinA*
Botox Cosmetic = Vistabel
BOTOX® Is the Most Widely Studied and Well-Characterized Neurotoxin...

- 26 indications in ~100 countries
- >115 sponsored studies with >21K patients; >50K treatments in trials
- 6,900+ peer-reviewed articles
- >1,000 colleagues touch BOTOX® every month...
- >80M vials distributed
- ~35,000 vials roll over the production line everyday...

Statistics reflect both BOTOX® and BOTOX® Cosmetic use.
Peer-Reviewed Publications (manuscripts, reviews, case reports) on BOTOX® and BOTOX® Cosmetic (data from Aug 2018).
### Clinical Studies Overview

<table>
<thead>
<tr>
<th>Objective</th>
<th>Dose-Ranging Study (10-002)</th>
<th>Pivotal Study 1 (142)</th>
<th>Pivotal Study 2 (143)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Areas</strong></td>
<td>FHL (with GL) (10 injection points)</td>
<td>FHL (with GL) (10 injection points)</td>
<td>FHL (with GL) and LCL (16 injection points)</td>
</tr>
</tbody>
</table>
| **Treatments** | 3 arms:  
- Botox 30U (10U FHL + 20U GL)  
- Botox 40 U (20U FHL + 20U GL)  
- Saline placebo | 2 arms:  
- Botox 40 U (20U FHL + 20U GL)  
- Saline placebo | 3 arms:  
- Botox 40 U (20U FHL + 20U GL)  
- Botox 64 U (20U FHL + 20U GL + 24U LCL)  
- Saline placebo |
| **Subjects/Sites** | 175 subjects (1:1:1)  
7 Sites (CAN) | 391 toxin-naïve subjects (3:1)  
16 sites (US, CAN, EU) | 787 toxin-naïve subjects (2:2:1)  
24 sites (US, EU) |

FHL: Forehead lines; GL: Glabellar lines; LCL: Lateral Canthal lines

Allergan Data on File
Dose-Ranging Study (10-002)
Treatment Overview

Study 10-002: Botox Cosmetic 30–40 U

Treatment: FHL + GL

- 2 or 4 Units Botox Cosmetic per site (vs placebo)
- **FHL – Botox 10 or 20 U in 5 sites**
- **GL – Botox 20 U in 5 sites**

- **Total:** Botox 30 or 40 U in 10 sites

FHL: Forehead lines, GL: Glabellar lines
Botox (onabotulinumtoxinA) Package Insert, Irvine, CA, Allergan, Inc. October 2017
Pivotal Study 142 Treatment Overview

**Study 142:** Botox Cosmetic 40 U

**Treatment:** FHL + GL

- 4 Units Botox Cosmetic per site (vs placebo)
- FHL – Botox 20 U in 5 sites
- GL – Botox 20 U in 5 sites

**Total:** Botox 40 U in 10 sites

FHL - Forehead lines; GL - Glabellar lines
Botox (onabotulinumtoxinA) Package Insert, Irvine, CA, Allergan, Inc. October 2017
Pivotal Study 143 Treatment Overview

Study 142: Botox Cosmetic 64 U

Treatment: FHL + GL + LCL

- 4 Units Botox Cosmetic per site (vs placebo)
- FHL – Botox 20 U in 5 sites
- GL – Botox 20 U in 5 sites
- LCL – Botox 24 U in 6 sites

- Total: Botox 64 U in 16 sites

FHL-Forehead lines; GL-Glabellar lines; LCL-Lateral Canthal lines
Botox (onabotulinumtoxinA) Package Insert, Irvine, CA, Allergan, Inc. October 2017
Primary Efficacy Analysis

FHL FWS ≥2-grade Composite Scores (max elevation) at Day 30

Study 142 – P-value ≤0.012 through Day 150

Study 143 – P-value ≤0.002 through Day 120

ITT Population:
FHL: Forehead lines; GL: Glabellar lines; LCL: Lateral Canthal lines; FWS: Facial Wrinkle Scale
Allergan Data on File
FHL FWS ≥2-grade Composite by Treatment Cycle

Study 142

Cycles 2 and 3: All groups treated with open-label Botox 40U (20U FHL + 20U GL)

Cycle 1

Cycle 2

Cycle 3

Study 143

Cycles 2 and 3: All groups treated with open-label Botox 64U (20U FHL + 20U GL + 24U LCL)

Cycle 1

Cycle 2

Cycle 3

% FHL Responders
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

Phase 3 Study of OnabotulinumtoxinA Distributed Between Frontalis, Glabellar Complex, and Lateral Canthal Areas for Treatment of Upper Facial Lines

KOENAAD DE BOULLE, MD,* WILLIAM PHILIP WERSCHLER, MD,† MICHAEL H. GOLD, MD, FAAD,‡ SUZANNE BRUCE, MD,§ GERHARD SATTLER, MD,¶ PATRICIA OGLIVIE, MD, PhD,¶ JAMES STREET, PhD,* KRISTEN E. LARSEN, PhD,* IRINA YUSHMANOVA, MD,** XIAOFANG LEE, PhD,** ELISABETH LEE, MPH,** DOMENICO VITARELLA, PhD,** AND CHERI MAO, MS**

BACKGROUND Although commonly practiced, simultaneous onabotulinumtoxinA injections to multiple facial areas have not been investigated in prospective studies.

OBJECTIVE Evaluate safety and efficacy of onabotulinumtoxinA for treatment of forehead lines (FHL) distributed between the frontalis (20 U) and glabellar complex (20 U), with or without simultaneous lateral canthal areas (crow’s feet lines [CFL], 24 U) treatment.

METHODS Subjects with moderate to severe FHL were randomized (2:2:1) to onabotulinumtoxinA 40 U, onabotulinumtoxinA 64 U, or placebo. After 180 days, subjects could receive up to 2 additional open-label onabotulinumtoxinA 64 U treatments.

RESULTS The intent-to-treat (ITT) population comprised 787 subjects, and the modified ITT (mITT) population (subjects with psychological impact) comprised 568. After 30 days, onabotulinumtoxinA 40 U and 64 U significantly improved investigator- and subject-assessed FHL severity by at least 2 Facial Wrinkle Scale (FWS) grades in 45.0% and 53.0% of ITT subjects, respectively, versus 0.0% receiving placebo (both, p < .0001). Significantly more mITT subjects receiving onabotulinumtoxinA achieved investigator- and subject-assessed FWS ratings of none/moderate versus placebo (p < .001). OnabotulinumtoxinA was well tolerated.

CONCLUSION OnabotulinumtoxinA distributed between the frontalis and glabellar complex, with or without additional CFL injections, was safe and effective for treatment of moderate to severe FHL.

Supported by Allergan plc. Writing and editorial assistance was provided by K.E. Larsen and J. Street of Peloton Advantage, Parsippany, NJ, and was funded by Allergan plc Dublin, Ireland. K. De Bouille has served as a consultant, on an advisory board and speakers’ bureau, and has received honoraria from Allergan plc. W.P. Werschler has served on an advisory board, as a speaker, and as a consultant and/or received research funding from Allergan plc. M.H. Gold serves as a consultant and has received research funding from Allergan plc. S. Bruce has served on an advisory board and on a speakers’ bureau, has received research grants, and serves as an investigator trainer for Allergan plc. G. Sattler has received a research grant for participation in this study. P. Ogilvie received research grants from Allergan plc and serves as a consultant, advisory board member, and trainer for Allergan plc. D. Vitarella was an employee of Allergan plc at the time of this study. J. Street and K.E. Larsen serve as medical writers for Peloton Advantage, which received funding for editorial services from Allergan plc. E. Lee, X. Lei, C. Mao, and I. Yushmanova are employees of Allergan plc and may own stock or options in the company. The authors have indicated no significant interest with commercial supporters.
Higher doses of Botox Cosmetic are well tolerated and offer better longevity than the traditional 20-unit dose, according the results of a new clinical study.

Trial 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 of 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.
Masseter Prominence

**Masseter Prominence:**
*Impressive BOTOX® Cosmetic Data*

**LOWER FACE**
Masseter Prominence
Approval Expected 2023

- Common beauty complaint
- Preference for contoured vs. rounded face
- Potential dosing more than 2X existing facial indications

**BOTOX® Cosmetic: Percent Change from Baseline**
Day 90 Masseter Volume as Measured by Computed Tomography
(Pre-Defined Region)

- **PLACEBO**
  - -2.1

- **24 U BOTOX**
  - -19.7

- **48 U BOTOX**
  - -22.3

- **72 U BOTOX**
  - -25.4

- **96 U BOTOX**
  - -25.6

**p < 0.001 vs. placebo**

**MEAN BASELINE TOTAL CT MASSETER MUSCLE VOLUME (CM3) OF DEFINED REGION**

- **27.6**
- **28.7**
- **29.2**
- **26.9**
- **29.3**

MMPS = Masseter Muscle Prominence Scale, mITT = modified Intent To Treat
Platysma Prominence: BOTOX Cosmetic Development to Rejuvenate Neck Appearance

Platysma Prominence: BOTOX® Cosmetic Development to Rejuvenate Neck Appearance

- Desired attribute: smooth neck & tightened jawline definition
- Improved neck contour supports Allergan’s comprehensive Facial Shaping Portfolio
- Potential dosing higher than existing facial indications

Images courtesy of Dr. S. Humphrey

NECK
Platysma Bands Approval Expected 2024
Botulinum Toxin Type E (BoNT/E)¹
Approval Expected 2024

Unique profile…
- Fast Onset
- Short Duration

…fulfills unmet need:
- Last-minute demand
- Introductory treatment for “considerers”

Glabellar lines early P2 dosing:
- Efficacy onset by 24 hours
- Duration 2-4 weeks

Complementary to BOTOX® Cosmetic

¹. Allergan has agreed to acquire Bontic; acquisition expected to close by the end of 2016, subject to the satisfaction of certain closing conditions.
Safety and Efficacy of EB-001, a Novel Type E Botulinum Toxin, in Subjects with Glabellar Frown Lines: Results of a Phase 2, Randomized, Placebo-Controlled, Ascending-Dose Study

Steve G. Yoel, M.D.
Sunil S. Dhawan, M.D.
Domenico Vitarelli, Ph.D.
Wajdie Ahmad, M.A.
Fadad Hasan, M.S.
Susan Abushakra, M.D.
Newport Beach and Paramount, Calif.

Background: Botulinum neurotoxins, which are widely used commercially for therapeutic and cosmetic applications, have historically belonged to serotypes A and B. Serotype E has a distinct profile with a faster onset and shorter duration of effect. EB-001 is a proprietary formulation of serotype E in development for aesthetic (cosmetic) and therapeutic uses.

Methods: This first-in-human, randomized, double-blinded, placebo-controlled, ascending-dose cohort study enrolled 42 subjects who received EB-001 (n = 30) or placebo (n = 7). The efficacy primary outcome was the proportion of subjects with a two-grade investigator-rated improvement in glabellar frown line severity at maximum frown. Safety evaluations included adverse events, laboratory tests, and physical examinations.

Results: A two-grade investigator-rated response was observed starting in the third cohort (EB-001), with increased rates observed at higher doses. Onset of clinical effect was within 24 hours, with a duration ranging between 14 and 30 days for the highest doses. Adverse event incidence was low, with the most common being mild to moderate headache. There were no serious adverse events or deaths, and there were no clinically significant changes in other safety assessments.

Conclusions: In this clinical study in glabellar frown lines, EB-001 showed favorable safety, tolerability, and dose-dependent efficacy, with an 80 percent response rate at the highest dose. The maximum clinical effect of EB-001 was seen within 24 hours and lasted between 14 and 30 days. This differentiated EB-001 profile supports its development for aesthetic and therapeutic applications where fast onset and short duration of effect are desirable. (Plast. Reconstr. Surg. 142: 847e; 2018.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, II.
BoNT/E1 Has 2 Unique Selling Propositions

**Starter Toxin**
65M considerers / 49% worried about an unnatural look

- Chance to test drive treatment

**Event Toxin**
1 of 4 BOTOX® users

- On-demand before events

Source: ADN Patient Questionnaire (n=173)

1. Allergan has agreed to acquire Boehringer Ingelheim’s botulinum toxin business, subject to the satisfaction of certain closing conditions.
Dysport

= 

Azzulare
Dysport
Botulinum toxin A - abobotulinumtoxinA

Dysport available in Europe
By 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
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
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

**INTRODUCTION**
- Two injection volumes (0.05 mL and 0.08 mL) of Xeomin® (abobotulinumtoxinA) (ABO) were used to treat glabellar lines in this study.
- The study was conducted to assess the safety and efficacy of these volumes.

**SUBJECTS and METHODS**
- This was a randomized, double-blind, placebo-controlled trial.
- Subjects were randomly assigned to receive 0.05 mL, 0.08 mL, or placebo injections.
- Subject satisfaction and safety were evaluated at baseline, day 30, and day 90.

**RESULTS**
- Subject satisfaction was assessed using a 7-point scale.
- The study concluded that both volumes were safe and effective.

**SUMMARY**
- The study results demonstrate that both volumes are effective in treating glabellar lines.
- Subject satisfaction was high, and there were no adverse events reported.

**Figures**
- Graphs showing changes in subject satisfaction over time.
- Comparison of satisfaction levels between the two injection volumes and placebo.

**ACKNOWLEDGMENTS**
- Study funded by Allergan, Inc.
Xeomin
=
BoCouture
Merz – Xeomin – NT201

- Approved in Europe for blepharospasm and spasmodic tortilcollis
- 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. crows feet, horizontal forehead lines
- high efficacy, safety and tolerability as assessed 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

Responders (Max Frown) at Day 30: Improvement of at least 2 points on BOTH: Investigator-Rated FWS AND Patient-Rated 4-Point Scale

Study GL-1

Diff RR: 0.60; 95% CI [0.52, 0.68]  
p<0.0001

Study GL-2

Diff RR: 0.48; 95% CI [0.40, 0.56]  
p<0.0001

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

Investigator: 1-Point Responders (Max Frown)

Week 4
- Observed Case: 99.0%
- Worst Case: 98.1%

Week 12
- Observed Case: 80.8%
- Worst Case: 80.0%

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 versus OnabotulinumtoxinA in the Treatment of Glabellar Facial Lines: Results from a Multicenter, Randomized, Double-Blinded Trial

Michael A.C. Kane, Michael H. Gold, William P. Coleman III, Derek H. Jones, Emila A. Tanghetti, Tina S. Alster, Tom E. Rohrer, Cheryl M. Burgess, and Ava T. Shamban

Manhattan Eye, Ear & Throat Hospital, New York, NY; Tennessee Clinical Research Center, Nashville, TN; Tulane Health Sciences Center, New Orleans, LA; Skin Care and Laser Physicians of Beverly Hills, Los Angeles, CA; Center for Dermatology and Laser Surgery, Sacramento, CA; Washington Institute of Dermatologic Laser Surgery, Georgetown University Hospital, Washington, DC; The Skin & Cancer Foundation of South Florida, Fort Lauderdale, FL; Army Medical Department Center and School, Fort Sam Houston, TX; University of California Los Angeles, Los Angeles, CA

INTRODUCTION

- IncobotulinumtoxinA is a well-established treatment for glabellar lines.
- Head-to-head comparison studies have demonstrated that incobotulinumtoxinA (IBTX) results in comparable safety and efficacy for both cosmetic and therapeutic uses.
- In 2011, IncobotulinumtoxinA was approved by the FDA for improvement in the appearance of moderate to severe glabellar lines with a recommended dosage of 25 units (b)
- This is the first large, real-world, randomized, double-blind, parallel-group study to compare the efficacy and safety of incobotulinumtoxinA vs. onabotulinumtoxinA in a single, 12-week trial to improve the appearance of glabellar lines.

TRIAL DESIGN

- Prospective, multicenter, randomized, double-blind, parallel group trial
- IncobotulinumtoxinA vs. onabotulinumtoxinA
- Randomization treatment allocation ratio 1:1
- Study Population
  - 494 females subjects with moderate-to-severe glabellar lines
  - 257 IBTX, 237 OBTX
  - Subjects received a single injection of study treatment at the 1 baseline site.
  - Mean age of 44.0 years for both groups
- Criteria:
  - ≥12.5 mm wrinkle depth
  - ≤20 units of chronological treatment
  - <4 mL of injection volume

ENDPOINTS

Primary Endpoint
- Response defined as ≥1-point improvement from baseline on the FWS at maximum frown 1 month post-treatment. (Photo assessment by Independent Panel Raters (IPR))

Secondary Endpoints
- ≥1-point improvement from baseline on the FWS at maximum frown 2, 3, and 4 months post-treatment. (Photo assessment by IPR)
- ≥1-point improvement from baseline on the FWS at maximum frown 1, 2, 3, and 4 months post-treatment. (Photo assessment by self-assessment)
- Subject assessment of treatment satisfaction at 1, 2, 3, and 4 months
- Subject reported date of onset and peak effect
- Safety assessment (Indications of adverse events)

Trial Enrollment

RESULTS

Efficacy Profiles by IPR

Similar Efficacy Profiles Were Demonstrated at All Timepoints as Assessed by Independent Panel Raters

TREATMENT EMERGENT ADVERSE EVENTS (TEAE) REPORTED OVER THE 4-MONTH STUDY

- Subjects with at least 1 TEAE: IncobotulinumtoxinA (IBTX) 14 (35.3%) vs. OnabotulinumtoxinA (OBTX) 19 (40.7%)
- Subjects with at least 1 TEAE of ≥3 severity: IBTX 7 (18.4%) vs. OBTX 9 (19.1%)

- Face: 2.0% in IBTX, 2.2% in OBTX
- Eye: 1.3% in IBTX, 1.2% in OBTX
- Hair: 0.6% in IBTX, 0.6% in OBTX
- Larynx and Trachea: 1.0% in IBTX

CONCLUSIONS

- The primary endpoint was met. Equivalence between incobotulinumtoxinA and onabotulinumtoxinA was demonstrated at 1-month (≥1-point improvement on FWS).
- Similar efficacy profiles between IncobotulinumtoxinA and onabotulinumtoxinA were demonstrated at all timepoints (1, 2, 3, and 4 months).
- Subjects reported satisfaction, Treatment Onset, and Peak Effect were similar between incobotulinumtoxinA and onabotulinumtoxinA.
- No difference in safety profiles between incobotulinumtoxinA and onabotulinumtoxinA.
- Adverse events were similar to previous botulinum toxin type A studies.
- IncobotulinumtoxinA and onabotulinumtoxinA result in similar efficacy and safety profiles for the treatment of glabellar facial lines.
PrabotulinumtoxinA

Background

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

Favors Botox®
Favors Nabota®

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

Non-inferiority Margin = -15%

Primary Endpoint
Responder Rate at Week 4

<table>
<thead>
<tr>
<th></th>
<th>Nabota®</th>
<th>Botox®</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=123#</td>
<td>N=117#</td>
<td></td>
</tr>
</tbody>
</table>

Secondary Endpoint
Glabellar Lines Severity at Maximum Frown by Investigator Assessment

<table>
<thead>
<tr>
<th></th>
<th>Nabota®</th>
<th>Botox®</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 weeks</td>
<td>93.6%</td>
<td>89.3%</td>
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<tr>
<td>8 weeks</td>
<td>83.9%</td>
<td>82.6%</td>
</tr>
<tr>
<td>12 weeks</td>
<td>75.6%</td>
<td>70.0%</td>
</tr>
<tr>
<td>16 weeks</td>
<td>62.1%</td>
<td>54.6%</td>
</tr>
</tbody>
</table>

Safety: Drug Related Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Nabota®</th>
<th>Botox®</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.9%</td>
<td>4.5%</td>
</tr>
<tr>
<td></td>
<td>(8/135)</td>
<td>(6/133)</td>
</tr>
</tbody>
</table>

P=0.60
**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

---

1. Jeuveau Package Insert Section 1.1
2. Jeuveau Package insert Section 2
U.S. Phase III Glabellar Line Studies

**Primary Endpoint**

**Composite Score**

*(Investigator and Subject agree)*

≥2 Point GLS Improvement at Maximum Frown on Day 30

![Composite Score Graph](image)

**Primary Endpoint Components**

≥2 Point GLS Improvement at Maximum Frown (Investigator and Subject Assessments)

<table>
<thead>
<tr>
<th></th>
<th>Investigator</th>
<th>Subject</th>
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</thead>
<tbody>
<tr>
<td><strong>EV001</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jeuveau™</td>
<td>77.5%</td>
<td>76.7%</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.2%</td>
<td>3.6%</td>
</tr>
<tr>
<td><strong>EV002</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jeuveau™</td>
<td>82.5%</td>
<td>76.3%</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.7%</td>
<td>4.0%</td>
</tr>
</tbody>
</table>

1. Data on file, CSR EV-001, pg 5, 68
2. Data on file, CSR EV-002, pg 5, 68
### U.S. Phase III Glabellar Line Studies

**Secondary Endpoints**

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

#### Day 120 Responder Rates

<table>
<thead>
<tr>
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<th>EV-001</th>
<th>EV-002</th>
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</thead>
<tbody>
<tr>
<td><strong>≥2 Composite Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jeuveau™</td>
<td>8.3*</td>
<td>12.4*</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.3</td>
<td>0</td>
</tr>
</tbody>
</table>

#### Day 150 Responder Rates

<table>
<thead>
<tr>
<th></th>
<th>EV-001</th>
<th>EV-002</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>≥2 Composite Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jeuveau™</td>
<td>4.6*</td>
<td>4.6*</td>
</tr>
<tr>
<td>Placebo</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*All p-values <0.05

---

1. Data on file CSR EV-001, pg 78;
2. Data on file, CSR EV-002, pg 78
Primary Endpoint: Non-Inferiority at Week 4 (GLS at Max Frown)

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

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

*The prabotulinumtoxinA formulation in this study is different than the Jeuveau™ formulation*

---

1. Data on file (CSR DWP450001, pg 78 & 55)
Efficacy and Safety of PrabotulinumtoxinA for the Treatment of Glabellar Lines in Adults Subjects: Results From 2 Identical Phase III Studies

KENNETH R. BEER, MD, ÁVA THERESA SHAMBAN, MD,† RUI L. AVELAR, MD,‡ JOHN E. GROSS, MD,§
AND ANNEKE JONKER, MSc∥ ON BEHALF OF THE EV-001/EV-002 STUDY GROUP

BACKGROUND PrabotulinumtoxinA is a 900 kDa botulinum toxin Type A produced by Clostridium botulinum.

OBJECTIVE To investigate the efficacy and safety of prabotulinumtoxinA for the treatment of glabellar lines.

MATERIALS AND METHODS Adult subjects (n = 330 in EV-001; n = 324 in EV-002) with moderate to severe glabellar lines at maximum frown on the 4-point Glabellar Line Scale (GLS; 0 = no lines, 1 = mild, 2 = moderate, and 3 = severe) were enrolled in 1 of 2 identical 150-day, double-blind, placebo-controlled, single-dose, Phase III studies. Subjects were randomized 3:1 to receive 20-U prabotulinumtoxinA or placebo. The primary efficacy end point was the proportion of responders on Day 30 where the investigator and subject independently agreed that a >2-point improvement had occurred on the GLS at maximum frown from Day 0. Adverse events (AEs) were evaluated throughout the study.

RESULTS Responder rates in the prabotulinumtoxinA and placebo groups were 67.5% and 1.2% in EV-001 and 70.4% and 1.3% in EV-002; absolute differences between groups were 66.3% and 68.1% in EV-001 and EV-002, respectively (both p < .001). No serious AE in either study was assessed as study drug related.

CONCLUSION In these studies, a single dose of 20-U prabotulinumtoxinA was safe and effective for the treatment of glabellar lines.

A. T. Shamban and K. R. Beer served as principal clinical trial investigators for the EV-001 and EV-002 studies. All participating co-investigators who formed the EV-001/EV-002 Study Group are listed in the acknowledgments. As sponsor of the EV-001 and EV-002 studies, Evolus, Inc., of Newport Beach, CA, was involved in the design of these studies and provided funding, study materials, equipment, and medications to all investigational sites. Evolus also provided funding to contract organizations involved in data collection, analysis, and reporting of the results. R. L. Avelar is the Head of R&D and Chief Medical Officer for Evolus, Inc., and receives compensation in salary, stock, and stock options. Before and during the time of these studies and manuscript preparation, J. E. Gross was the Chief Scientific Officer at Evolus, Inc.; he will receive royalty and milestone payments should the product be approved. Anneke Jonker of Medical Writing Associates, West Vancouver, BC, Canada, provided technical assistance with manuscript preparation and submission; she holds stock in Evolus, Inc.
## Jeuveau™ Safety

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

### U.S.: Adverse Events¹

<table>
<thead>
<tr>
<th></th>
<th>US PIII EV-001</th>
<th>US PIII EV-002</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Jeuveau™</td>
</tr>
<tr>
<td>All</td>
<td>32.1’</td>
<td>38.2’</td>
</tr>
<tr>
<td>Related</td>
<td>13.1’</td>
<td>15.4’</td>
</tr>
</tbody>
</table>

• Other AE’s of Interest
  – Ptosis (related)
    • EV-001 – eyelid 0.8%, eyebrow 0.4%
    • EV-002 – eyelid 1.2%, eyebrow 0.4%

### EU/CAN: Adverse Events²

<table>
<thead>
<tr>
<th></th>
<th>EU/CAN PIII 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>

• Other AE’s of Interest
  – Ptosis (related)
    • Eyelid – Jeuveau™ 1.6%, Botox® Cosmetic 0%
    • Eyebrow – Jeuveau™ 0.0%, Botox® Cosmetic 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 antibodies³
- Vacuum Dried Formulation (commercial formulation): No cases of seroconversion

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1. Data on file (CSR EV-001, pg 100 & 107; CSR EV-002, pg 100 & 107)
2. Data on file (CSR EVB-003, pg 8)
3. Jeuveau Package Insert, Section 6.2

PLEASE SEE APPROVED USE AND IMPORTANT SAFETY INFORMATION INCLUDING BOXED WARNING 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

Berthold-Josef Rzany, MD, ScM, Benjamin Ascher, MD, Rui L Avelar, MD, Jesper Bergdahl, MD, Vince Bertucci, MD, Isaac Bodo, 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 ▼
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 Patients

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Abstract

Background: PrabotulinumtoxinA is a 900 kDa botulinum toxin type A produced by Clostridium botulinum.

Objectives: The authors sought to investigate the efficacy and safety of prabotulinumtoxinA compared to onabotulinumtoxinA and placebo for the treatment of glabellar lines.

Methods: This was a 15-day, multicenter, double-blind, controlled, single-dose Phase III study. Adult patients (n = 540) with moderate to severe glabellar lines at maximum frown as assessed by the investigator on the validated 4-point Glabellar Line Score (0 = no lines, 1 = mild, 2 = moderate, 3 = severe), who also had that their glabellar lines had an important psychological impact, were enrolled. Patients were randomized 1:1:1 to receive a single treatment (0.1 mL divided into each of 5 glabellar sites) of 20 U prabotulinumtoxinA (n = 243), 20 U onabotulinumtoxinA (n = 243), or placebo (n = 49). The primary efficacy endpoint was the proportion of responders (patients with a Glabellar Line Score of 0 or 1 at maximum frown by investigator assessment) up to day 30.

Results: Responder rates for the primary efficacy endpoint were 87.2%, 82.8%, and 4.2% in the prabotulinumtoxinA, onabotulinumtoxinA, and placebo groups, respectively. The absolute difference between prabotulinumtoxinA and onabotulinumtoxinA groups was 4.4% (95% confidence interval [1.5, 10.8]). Given that the lower bound of the 95% confidence interval for the difference was less than -5.0%, non-inferiority of prabotulinumtoxinA vs onabotulinumtoxinA was concluded. Five patients (2 prabotulinumtoxinA, 1 onabotulinumtoxinA, 2 placebo), 2 placebo- and 20 U prabotulinumtoxinA-experienced serious adverse events, none of which were study drug related.

Conclusion: A single treatment of 20 U prabotulinumtoxinA was safe and effective and non-inferior to 20 U onabotulinumtoxinA for the treatment of moderate to severe glabellar lines.
Jeuxveau™ EU/CA Phase III Trial

Glabellar Line Study Design

■ Study Design
  Multi-center, blinded, randomized, single dose study, 150 days
  N = 540, randomized 5:5:1 (Jeuxveau™ : 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)
Glabellar Line Study Design

- **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
Jeuveu™ EU/CA Phase III Trial

Glabellar Line Study Design

**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
- ∆ to D 90, mean HADS Anxiety (HADS-A)
- ∆ to D 90, mean HADS Depression (HADS-D)

IA: Investigator Assessment
SA: Subject Assessment
Jeuveau™ EU/CA Phase III Trial

**Primary Endpoint: Non-Inferiority**

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

![Bar Chart]

- **Jeuveau™**: 87.2%
  - n=235
- **Botox**: 82.8%
  - n=244
- **Placebo**: 4.2%
  - n=48

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

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

Source: Data on file (CSR EVB-003, pg 5-6)
## Secondary Endpoints

**≥1 Improvement GLS at Maximum Frown Investigator Assessment**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Botox</th>
<th>Jeuveau™#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 2</td>
<td>12.20%#</td>
<td>57.00%#</td>
<td>54.2%*#</td>
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</table>

<table>
<thead>
<tr>
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<th>Placebo</th>
<th>Botox</th>
<th>Jeuveau™#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 150</td>
<td>8.30%#</td>
<td>34.40%#</td>
<td>37.7%*#</td>
</tr>
</tbody>
</table>

**Subject Satisfaction**

**≥1 Improvement Subject Satisfaction**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Botox</th>
<th>Jeuveau™#</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)
Jeuveau™ EU/CA Phase III Trial
Exploratory Endpoint

Jeuveau™ vs Botox
≥1 Pt Improvement of GLS at Maximum Frown

Investigator Assessment

Subject Assessment
Jeuveau™ EU/CA Phase III Trial

Exploratory Endpoint

Jeuveau™ vs Botox
Global Aesthetic Improvement Scale

Investigator Assessment

Subject Assessment

Positive Responders on the G A I S (%) vs Days Post Treatment

Investor Presentation
Jeuveau™ A EU/CA Phase III Trial

Exploratory Endpoint

Jeuveau™ vs Botox

Subject Satisfaction

Positive Responders on the SSS (%)

Source: Data on file (CSR EVB-003, pg 89)

Investor Presentation
30 new exploratory head-to-head data points

GLS IMPROVEMENT
INVESTIGATOR ASSESSMENT

GLOBAL AESTHETIC IMPROVEMENT SCALE
INVESTIGATOR ASSESSMENT

SUBJECT SATISFACTION

GLS IMPROVEMENT
SUBJECT ASSESSMENT

GLOBAL AESTHETIC IMPROVEMENT SCALE
SUBJECT ASSESSMENT
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
DaxibotulinumtoxinA
Highly purified, botulin toxin type A molecule

Unique
EXCIPIENT
Patented Stabilizing Peptide
Positively charged peptide that binds with negatively charged area of molecule.
NO animal-derived components or human albumin

Two
‘DAXI’ MODALITIES

Current Focus

DaxibotulinumtoxinA for Injection (RT002)
In late-stage development
Designed to be long lasting, injectable neuromodulator

DaxibotulinumtoxinA Topical Gel (RT001)
In preclinical development
Designed to offer topical delivery of botulinum toxin

Potential for Better, Longer, Safer Treatment
What is the Peptide?

The peptide excipient (RTP004\textsuperscript{a}) is a 35 AA cell penetrating peptide (CPP)

An excipient is a component of a formulation that does not have direct biological/physiological effects

- **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**

\textsuperscript{a}Revance Therapeutics, data on file

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
BELMONT¹ 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 Lines: A Phase 2, Randomized, Dose-Ranging, Double-Blind, Multicenter Comparison With OnabotulinumtoxinA and Placebo

JEAN CARRUTHERS, MD,* NOVELL SOLISH, MD,1 SHANNON HUMPHREY, MD,1 NATHAN ROSEN, MD,1 CHANNY MUHIN, MD,1 VINCE BERTUCCI, MD,9 ARTHUR SWIFT, MD,9 ANDREI METELITS, MD,9,10 ROMAN G. RUBIO, MD,10 JACOB WAUGH, MD,11 JOHN QUIRING, PhD,12 GILL SHEARS, PhD,13 AND ALASTAIR CARRUTHERS, MD1

BACKGROUND Injectable daxibotulinumtoxinA (RT002) is an investigational botulinum toxin Type A in clinical development. It is formulated with a proprietary peptide and offers the potential of a longer acting neurotoxin therapy.

OBJECTIVE To compare the safety, efficacy, and duration of response of daxibotulinumtoxinA with onabotulinumtoxinA and placebo [ClinicalTrials.gov NCT02303002].

METHODS In this Phase 2, randomized, dose-ranging, parallel-group, double-blind, multicenter study, subjects with moderate or severe glabellar lines at maximum frown were randomly assigned to 20U, 40U, or 60U daxibotulinumtoxinA, 20U onabotulinumtoxinA, or placebo. Glabellar line severity was evaluated by investigators and subjects at least every 4 weeks, for at least 24 weeks.

RESULTS Overall, 208 subjects enrolled. Statistical and clinical superiority were observed for 40U and 60U daxibotulinumtoxinA over 20U onabotulinumtoxinA for a range of efficacy outcomes despite the study not being powered to detect statistically significant differences between these active treatment groups.

CONCLUSION The 40U dose of daxibotulinumtoxinA was well tolerated (e.g., absence of ptosis) and had the most favorable risk:benefit profile. Compared with 20U onabotulinumtoxinA, it exhibited a significantly greater response rate and a significantly longer duration of response (median of 24 weeks vs 19 weeks; p = .030).

Supported by Revance Therapeutics, Inc. J.D. Carruthers is a consultant and researcher for Revance, Allergan, Merz, and Alphaeon. N. Solish received a grant from Revance for participating in this study and is a consultant to Revance, Allergan, and Galderma. S. Humphrey has received research grants from Revance Therapeutics. V. Bertucci is a consultant to, and receives payment for lectures, including service on speaker bureaus, from Allergan, Galderma, and Merz. He is also an investigator for Allergan, Galderma, Alphaeon, Merz, and Revance. A. Swift received an investigator fee from Revance Therapeutics, Inc. A. Metelits has been a consultant for Galderma and Merz. R.G. Rubio is an employee of, and holder of stock/stock options in, Revance Therapeutics, Inc. J. Waugh was an employee of, and held stock/stock options in, Revance Therapeutics, Inc. J. Quiring is an employee of QST Consultations, Ltd., which has received fees from Revance Therapeutics, Inc. for performing statistical analyses. G. Shears is an employee of, and has received fees from, Revance Therapeutics, Inc. for medical writing services. A. Carruthers is a consultant and researcher for Revance, Allergan, Merz, and Alphaeon. The remaining authors have indicated no significant interest with commercial supporters. DaxibotulinumtoxinA is an investigational agent.
SAKURA Phase 3 Clinical Development Program

**SAKURA 1**
Pivotal: 36 Weeks, Placebo-controlled Single treatment

<table>
<thead>
<tr>
<th></th>
<th>N = 303</th>
<th>Treatment Centers: 15*</th>
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<tbody>
<tr>
<td>DAXI</td>
<td>201</td>
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<tr>
<td>Placebo</td>
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**SAKURA 2**
Pivotal: 36 Weeks, Placebo-controlled Single treatment

<table>
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<tr>
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<tr>
<td>Placebo</td>
<td>102</td>
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</tbody>
</table>

**SAKURA 3**
Open-Label, Long-term Safety: 84 Weeks

<table>
<thead>
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<th>N = 2,691</th>
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<tbody>
<tr>
<td>Treatment Centers</td>
<td>65**</td>
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</table>

- DAXI Treatment Cycle 1 (36 wks) 2,380
- DAXI Treatment Cycle 2 (36 wks) 882
- DAXI Treatment Cycle 3 (12 wks) 568

Total Number of DAXI Treatment Cycles 3,830

In total over 2,800 patients received more than 4,200 DAXI 40U treatments across Phase 1 – 3 GL program

*U.S. only
**U.S. and Canada
A prospective, 84 week Open-Label, Repeat Dose Study evaluating the Safety and Effectiveness of DaxibotulinumtoxinA for Injection to Treat Moderate-to-Severe Glabellar Lines conducted at 66 sites across U.S. and Canada.
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

<table>
<thead>
<tr>
<th></th>
<th>SAKURA 1 and 2</th>
<th>SAKURA 3 OLS</th>
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<tbody>
<tr>
<td>Pooled Placebo</td>
<td>73.6*</td>
<td>73.2</td>
</tr>
<tr>
<td>SAKURA 1 (n=201)</td>
<td>74.0*</td>
<td>77.7</td>
</tr>
<tr>
<td>SAKURA 2 (n=204)</td>
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<td>79.6</td>
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<tr>
<td>OLS Treatment 1 (n=2380)</td>
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<tr>
<td>OLS Treatment 2 (n=882)</td>
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<tr>
<td>OLS Treatment 3 (n=568)</td>
<td>79.6</td>
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</table>

* p<0.001 vs placebo of 0% (SAKURA 1) and 1% (SAKURA 2)
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

Data shown include Treatment 1 for OLS Group B (i.e., De Novo + Received Placebo in SAKURA 1 or 2), Treatment 2 for both Groups A and B, and results from SAKURA 1 and 2 studies.
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

Data shown are for the first two Treatments of OLS Group B (i.e., De Novo + Received Placebo in SAKURA 1 or 2), and results from SAKURA 1 and 2 studies.
SAKURA 3 OLS confirmed the safety profile of DaxibotulinumtoxinA for Injection (DAXI) 40U established in the SAKURA 1 and 2 pivotal studies, with no new tolerability or safety concerns reported, and stable or decreasing rates of AEs following repeat dosing from treatment cycle 1 through treatment cycle 3.

- A total of 3830 DAXI treatments with DAXI 40U were administered to 2691 subjects in SAKURA OLS.
- No evidence of cumulative AEs over 3 treatment cycles, suggesting the safety profile of DAXI remained stable after repeated dosing.

Adverse Events (AEs) regardless of causality were experienced in a similar proportion of subjects (39%) in SAKURA 3 OLS, which enrolled 2691 subjects, compared with the placebo-controlled SAKURA 1 and 2 studies (41%) with 406 subjects who received DAXI 40U.

- Majority of AEs were mild in severity with most considered to be unrelated to treatment.
- The most common AEs reported were headache (5.9% subjects), nasopharyngitis (4.4%) and injection site pain (3.9%).
- Serious AEs occurred at a similar rate in SAKURA 3 OLS (1.1%) as in SAKURA 1 and 2 (1.0%) and none were related to treatment across the entire SAKURA program.
Safety Summary – 2
DaxibotulinumtoxinA for Injection

Treatment-related Adverse Events were experienced in fewer treatments (≈14%) in SAKURA 3 OLS across 66 clinical trial sites, compared with the pivotal SAKURA 1 and 2 studies (≈18%) conducted at 30 sites.

- The most frequently occurring treatment-related AEs were headache (4.6% of subjects), injection site pain (3.6%) and injection site erythema (3.0%) and no treatment related SAEs were observed across the entire SAKURA program.

- Progressively lower percentages of subjects experienced treatment-related AEs following successive treatments: Treatment cycle 1 = 16.8%, Treatment cycle 2 = 9.8%, and Treatment cycle 3 = 7.0%.

Eyelid Ptosis

- Low rate of eyelid ptosis observed of 0.9% (34 treatment-related events in 3830 treatments), and occurred in 1.3% of subjects at 66 sites. This compares to a rate of 2.2% in 405 subjects treated in SAKURA 1 and 2.
  - Rate decreased with subsequent DAXI treatment cycles: Treatment 1 = 1.0%; Treatment 2 = 0.8%; Treatment 3 = 0.7%
  - All but one eyelid ptosis was unilateral in presentation; the majority (85%) were mild in severity with a median duration of 44 days.

SAKURA®

revance
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, 50, 200, 150 U), Thailand (50, 100, 200 U), Philippines (100 U), India (100 U), Vietnam (100 U), China (Phase III), 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)

Meso/Latin America:
- Peru (100 U), Uruguay (100 U), Paraguay (100 U), Bolivia (50, 100, 200 U), Chile (50, 100, 200 U), Colombia (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)
# Brand Name by Country

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulax®</td>
<td>Azerbaijan, Georgia, India, Kuwait, Mongolia, Paraguay, Philippines, Russia, Thailand, Ukraine, Uruguay, Vietnam</td>
</tr>
<tr>
<td>Botulim®</td>
<td>Brazil</td>
</tr>
<tr>
<td>Hugel Toxin®</td>
<td>Thailand</td>
</tr>
<tr>
<td>Juvenlife®</td>
<td>Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Panama</td>
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<tr>
<td>Magnion®</td>
<td>Colombia, Ecuador</td>
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<tr>
<td>Reage®</td>
<td>Peru, Bolivia, Chile</td>
</tr>
<tr>
<td>Zentox®</td>
<td>Philippines</td>
</tr>
<tr>
<td>-</td>
<td>Taiwan (Recently approved)</td>
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</table>
**Clinical Study for Glabellar Lines**

**Comparative clinical study of Botulax® with Botox® for the improvement in Glabellar Lines**

**Improvement in Glabellar Lines at Maximum Frown**

<table>
<thead>
<tr>
<th></th>
<th>FAS (Full Analysis Set)</th>
<th>PPS (Per-Protocol Set)</th>
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<tbody>
<tr>
<td></td>
<td>Botulax®</td>
<td>Botox®</td>
</tr>
<tr>
<td>FAS N=134</td>
<td>90.30</td>
<td>81.34</td>
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<tr>
<td>PPS N=122</td>
<td>89.34</td>
<td>81.86</td>
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</table>

**Subjects**
Two hundred seventy two (272) healthy male/female adult patients aged between 18 and 65 with moderate to severe glabellar lines at maximum frown.

**Methodology**
A multicenter, double-blind, randomized, active-controlled comparative, Phase III clinical trial.

**Safety**
There was no noticeable difference in the safety profile between Botulax® and Botox®.

**Conclusion**
This clinical trial proved that the glabellar line improvement effect of Botulax® is not inferior to that of Botox® in patients with moderate to severe glabellar lines. Therefore, Botulax® is considered to be an effective and safe treatment option other than Botox®.
For more information regarding these clinical studies, please visit: [https://www.clinicaltrials.gov/](https://www.clinicaltrials.gov/)

<table>
<thead>
<tr>
<th>Row</th>
<th>Saved</th>
<th>Status</th>
<th>Study Title</th>
<th>Conditions</th>
<th>Interventions</th>
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<td>1</td>
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<td>Recruiting</td>
<td><strong>Evaluate the Safety and Efficacy of Botulax® as Compared to Botox® in Subject With Moderate to Severe Crow’s Feet Lines</strong></td>
<td>• Crow's Feet Lines</td>
<td>• Drug: Botulinum toxin type A</td>
<td>• Hugel Seoul, Korea, Republic of</td>
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</table>
Clinical Trials in USA. Status: Active

For more information regarding these clinical studies, please visit: [https://www.clinicaltrials.gov/](https://www.clinicaltrials.gov/)

<table>
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<tr>
<th>Status</th>
<th>Study</th>
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<tr>
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<td><strong>Botulinum Toxin Treatment of Glabellar Lines: Efficacy and Safety Study II</strong></td>
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<tr>
<td></td>
<td>Condition: Glabellar Frown Lines</td>
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<td>Interventions: Drug: Botulinum Toxin A; Drug: Placebo</td>
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<tr>
<td>Active, not recruiting</td>
<td><strong>Botulinum Toxin Treatment of Glabellar Lines: Efficacy and Safety Study I</strong></td>
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<td>Condition: Glabellar Frown Lines</td>
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<tr>
<td></td>
<td>Interventions: Drug: Botulinum Toxin A; Drug: Placebo</td>
</tr>
</tbody>
</table>
www.clinicaltrials.gov info CROMA Phase 3 studies

Botulinum Toxin Treatment of Glabellar Lines: Efficacy and Safety Study I & II

Randomized Double Blind Phase 3 Study to Assess the Efficacy and Safety of BoNT/A-DP in the Treatment of Glabellar Lines in Comparison With Placebo Followed by an Open Label Extension Study – two studies identical in their design

The aim of these studies is to assess the efficacy and safety of BoNT/A-DP in the treatment of glabellar lines in comparison with placebo, including efficacy after repeat treatments and long term safety

Trial Centre locations:
BLESS I: USA, DE, PL; clintrials.gov identifier: NCT02677298; planned 700 subjects
BLESS II: USA; clintrials.gov identifier: NCT02677805; planned 200 subjects
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
Outcome Measures

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, SAes and AESIs [Time Frame: through study completion (60 weeks)]
   Ages Eligible for Study: 18 Years to 75 Years; both sexes

INN: letibotulinumtoxinA
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