What's New With Liquid Toxins - And Other New Ideas for Toxins

South Beach Symposium
Miami Beach, FL

February 8 - 11, 2024

Presented by Michael H. Gold, MD
Gold Skin Care Center
Tennessee Clinical Research Center
Nashville, TN 37215

Academic Appointments

01. Assistant Clinical Professor

- Department of Medicine, Division of Dermatology, Nashville, TN USA
- Vanderbilt University School of Medicine: 2006-2014
- Vanderbilt University School of Nursing: 2006-2020

02. Adjunct Assistant Professor

- Meharry Medical College: 2013 – Present
- School of Medicine, Nashville, TN

03. Visiting Professor of Dermatology

- Huashan Hospital, Fudan University (Shanghai Medical University), Shanghai, China
- The First Hospital of China Medical University, Shenyang, China:
- Guangdong Provincial People's Hospital, Guangzhou, Zhejiang

04. Visiting Professor of Plastic Surgery

- First People's Hospital of Foshan University, Guangdong, China
- The First Affiliated Hospital of Zhejiang University, Hangzhou, Zhejiang
- Rongjun Hospital, Jiaxing, China
- The People's Hospital of Hunan Province, Changsha, China

05.

- Editor-in-Chief – Journal of Cosmetic Dermatology – Wiley: 2016-Present
- Editor-in-Chief- Dermatological Reviews – Wiley: 2019 - Present

Conflict of Interest

01. Consultant to many pharmaceutical, cosmeceutical, laser and energy-based device companies

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

03. For the benefit of this presentation, consultant, Investigator, Speaker for Galderma

Cosmetic Dermatology

- Toxins

  - Allergan Aesthetics - Botox Cosmetic*
  - 2022 – Botulinum Toxin Type E to be developed – studies underway

  - MedyTox (South Korea) – Neuronox/Siax
  - 2013 – MedyTox licensing agreement with Allergan to market Neuronox outside of Korea/Japan
  - 2020 – liquid toxin to be developed (?) – Innotox (liquid), Coretox (pure toxin)
    2024 – Formation of a new company – Luvantas – a subsidiary of MedyTox – to develop liquid toxin

  - Ipsen, Medicis (Valeant), now Galderma – Dysport*, Azzulare
  - 2022 – Galderma – liquid toxin development – approved in EU in 2021 (Alluzinace); second one being developed for the US market (QM)
  - 2020 – Ipsen – several new toxins in development –
  - modified Type A light chain (retarget to non-neuronal SNAP23
  - modified Type A for longer duration
  - modified Type B for improved binding affinity
  - recombinant Type B for faster acting, shorter duration
  - targeted secretion inhibitors for a wide range of applications

*2024 – Toxins Available in the US

Cosmetic Dermatology

- Toxins

  - Mentor (J&J) – PurTox – 2014 J&J pulls PurTox
  - Merz Aesthetics – Xeomin*, BoCouture
  - Hugel (South Korea) – Botulax
  - 2014 – marketing agreement with Croma – Letybo introduced into the EU, Canada, and Australia – pending US approval
    - Croma to market in EU
    - Hugel US to market in US, Canada, and Australia
  - ChinaTox – a variety of toxins available from China
  - Lanzhou Biological Products Institute – real
  - Others – not real
  - Relatox – 1st Russian Toxin - ?real
  - Evolus – Jeuveau* Neucevia+ in EU
  - Revance – daxibotulinum toxin A – Daxxify

*2024 – Toxins Available in the US

Cosmetic Neuromodulator Generic Names

- Botox Cosmetic -- onabotulinumtoxinA
- Dysport -- abobotulinumtoxinA
- Xeomin – incobotulinumtoxinA
- Jeuveau - prabotulinumtoxinA
- Daxxify – daxibotulinumtoxinA
- Letybo– letibotulinumtoxinA – US approval 2023, 2024?
- Galderma Liquid Toxin – relabotulinumtoxinA – US approval 2024?
- Luvantas – Liquid Toxin – nivobotulinumtoxinA - new application filed in US

Liquid Toxins in 2024

- Do Liquid Toxins – pre-mixed and ready to go – have a role for those injecting toxins?
- What do we know already?
- What does the data show?
- We will answer these questions today!

Why?

Innovation

- Ready to use; designed to be liquid from inception to injection
- Free from HSA, preservatives, animal-derived proteins, and lactose
- Novel syringe technology

Precision

- Optimized, precise concentration
- Consistency in dosing
- Comfort for HCPs; inject by volume—no need to count units

Performance

- Delivers the highest amount of active BoNT-A per recommended dose without sacrificing tolerability
- Robust clinical evidence
- Rapid onset, duration up to 6 months, improved patient well-being, safety

BoNT-A, botulinum toxin type A; HCP, healthcare professional; HSA, human serum albumin.

Formulation, Storage, and Handling[1]

- Developed without any human- or animal-derived excipients (HSA and lactose)
- Contains only plant and synthetic excipients shown to maintain toxin activity in a liquid preparation
- Shelf life of 12 months for unopened vials
- Store in a refrigerator (2–8 °C) in the outer carton to protect from light
- Do not freeze

HAS, human serum albumin.

1. Alluzience Summary of Product Characteristics 2021.

AbobotulinumtoxinA Solution

liquid formulation and **does not require reconstitution**, providing an innovative and convenient, ready-to-use aesthetic treatment for consistent and precise dosing

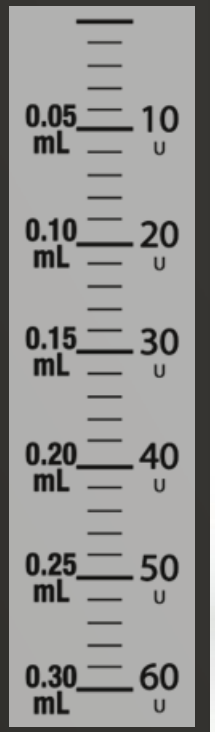
- The 125-U vial contains
  - 0.63-mL solution
  - 200 U/mL
- Indicated for temporary improvement of glabellar lines
  - Alluzience is approved in the EU
  - Dose: 50 U, 0.05 mL/injection point, 10 U/injection site
- Comes with the ABO syringe (optional use)
  - Clear markings every 10 units or 0.05 mL

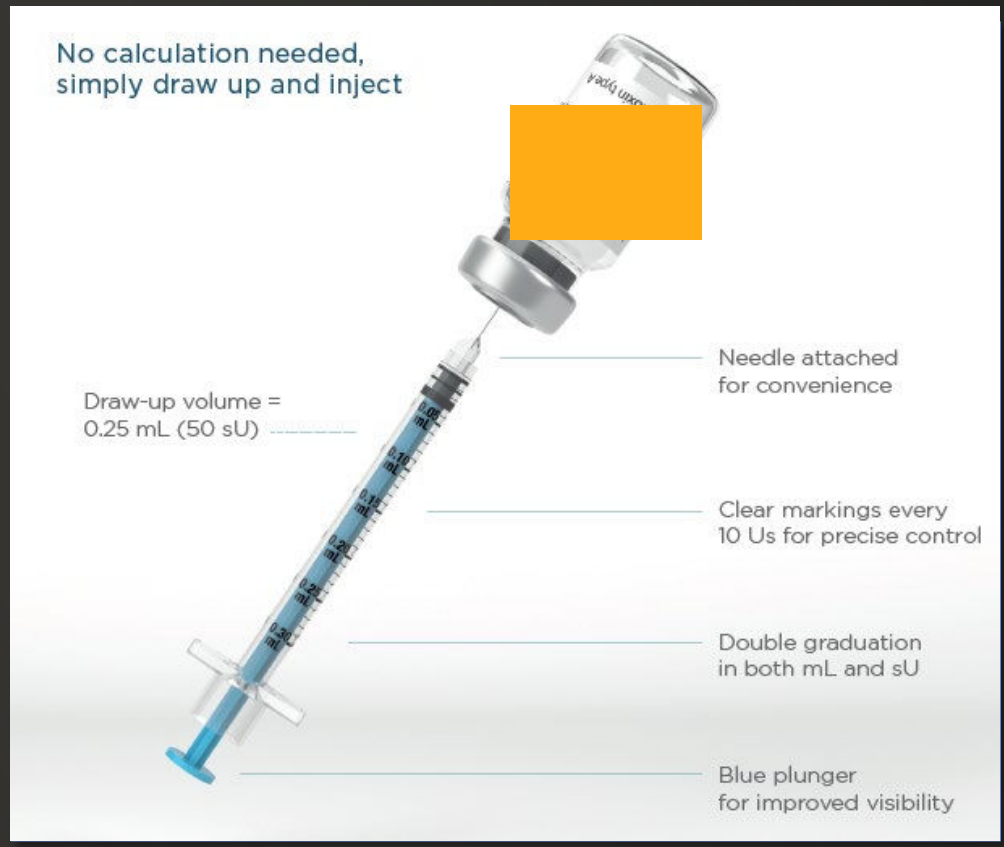
ABO, abobotulinumtoxinA.

ABO Syringe

The new ABO syringe (31G, 5/16" long) is designed for **optimal dosing** of **Alluzience**

- The graduation scale of the ABO syringe is presented in **both millilitres and units**, with clear markings every 0.05 mL or 10 units to facilitate accurate dosing of every single injection





Injectors simply draw up the recommended dose for glabellar lines (0.25 mL of solution or 50 Speywood units) and administer IM into 5 injection sites
(0.05 mL, 10 Speywood units per site)

ABO, abobotulinumtoxinA; IM, intramuscular.

Precision Key Takeaways

Precise neuromodulation for enhanced predictability

- Liquid formulation does not require reconstitution, providing an innovative and convenient, ready-to-use aesthetic treatment for consistent and precise dosing1
- Prediluted to optimised concentration
  - Allows injectors to move away from counting units and focus on volume of injection
- Delivers more active BoNT-A per recommended dose than onabotulinumtoxinA or incobotulinumtoxinA
- Comes with ABO syringe (optional use)

ABO, abobotulinumtoxinA; BoNT-A, botulinum neurotoxin type A.

1. Alluzience Summary of Product Characteristics 2021.

Clinical Development

	Study 146[1] (Phase 2)	Pooled Data: Study 189[2]	Pooled Data: Study 214 (placebo-controlled)	Study 214 (open-label, LTE)
Study population	Adults with moderate-to-severe glabellar lines	Adults with moderate-to-severe glabellar lines	Adults with moderate-to-severe glabellar lines	Adults with moderate-to-severe glabellar lines
Study design	Phase 2, randomized, DB	Phase 3, randomized, DB	Phase 3, randomized, DB	Open-label, long-term extension
Treatment	Alluzience 20 U, 50 U, 75 U	Alluzience 50 U		
Comparator	Dysport 50 U, Placebo	Placebo	Placebo	None
Number of patients	176	185	190	595[b]
Study duration, mo	Single treatment, 4-mo follow-up	Single treatment, 6-mo follow-up	Single treatment, 3-mo follow-up	Up to 5 treatments Total follow-up 15 mo
Primary endpoints	Responders[a] at day 29	Responders[a] at day 29		NA
Secondary endpoints	Responders[a] and reduction ≥2 severity grades at each post-treatment visit (ILA, max frown and at rest); day 29 responders who remained responders on day 113	*Study 189 and Study 214:* Responders at each post-treatment visit; day 29 responders who remained responders on days 57 onwards; responders (ILA) max frown and at rest *Study 189 only:* reduction ≥2 severity grades at each post-treatment visit		Responders[a] at each post-treatment visit (max frown and at rest)

DB, double-blind; ILA, investigator live assessment; LTE, long-term extension; NA, not applicable.
[a]Severity grading of glabellar lines as none or mild at maximal frown; [b]Included an additional 400 de novo subjects who did not take part in the placebo-controlled period.

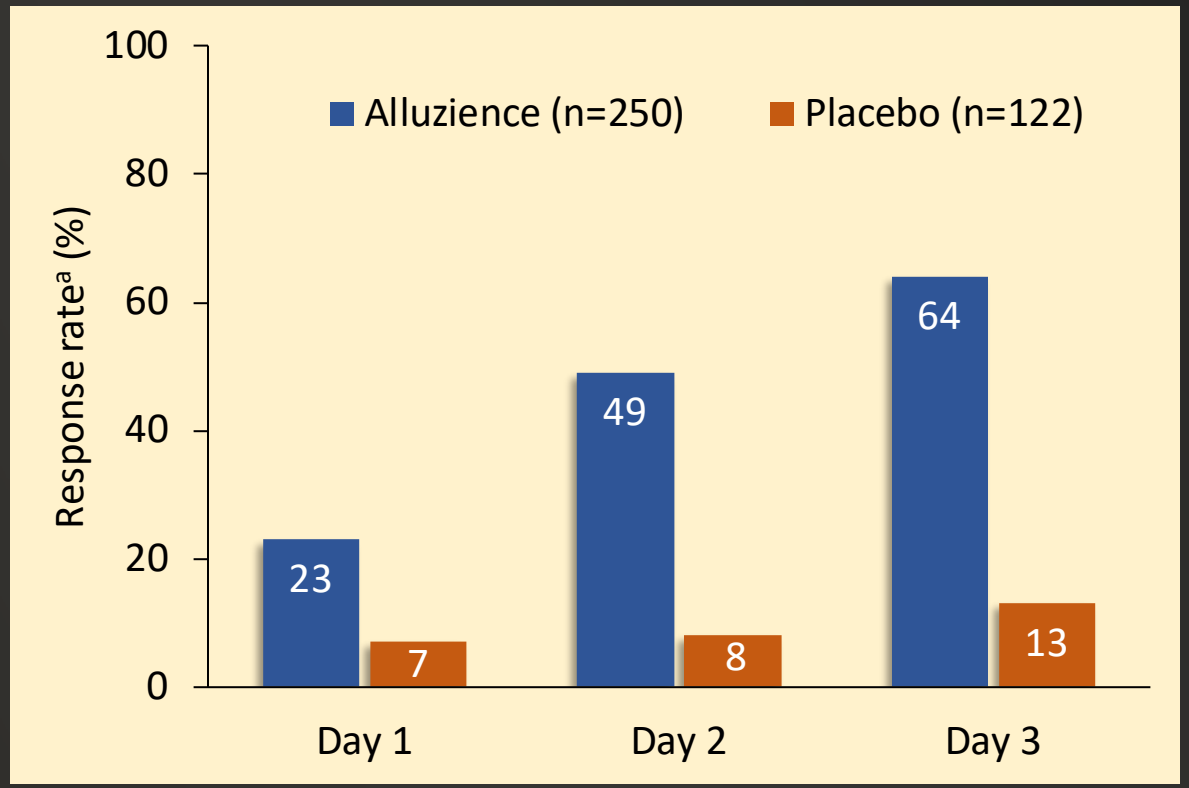
1. Ascher B, et al. *Aesthet Surg J*. 2018;38:183-1911;
2. Ascher B, et al. *Aesthet Surg J*. 2020;40:93-104

Rapid Onset of Effect – Results Within 24 Hours

Onset of response[a] was seen as early as 24 hours in 23% of patients after the initial treatment[1,2]

- Proportion with onset of response[a] on day 1:
  - **Alluzience: 23%**
  - Placebo: 7%
- Median time to onset of treatment response:
  - **Alluzience: 3.0 days** (*P*<0.0001 vs placebo)
  - Placebo: Not calculable

'The majority of patients reported an effect within 2 to 3 days'[1]



Pooled Phase 3 data from Studies 189 and 214.

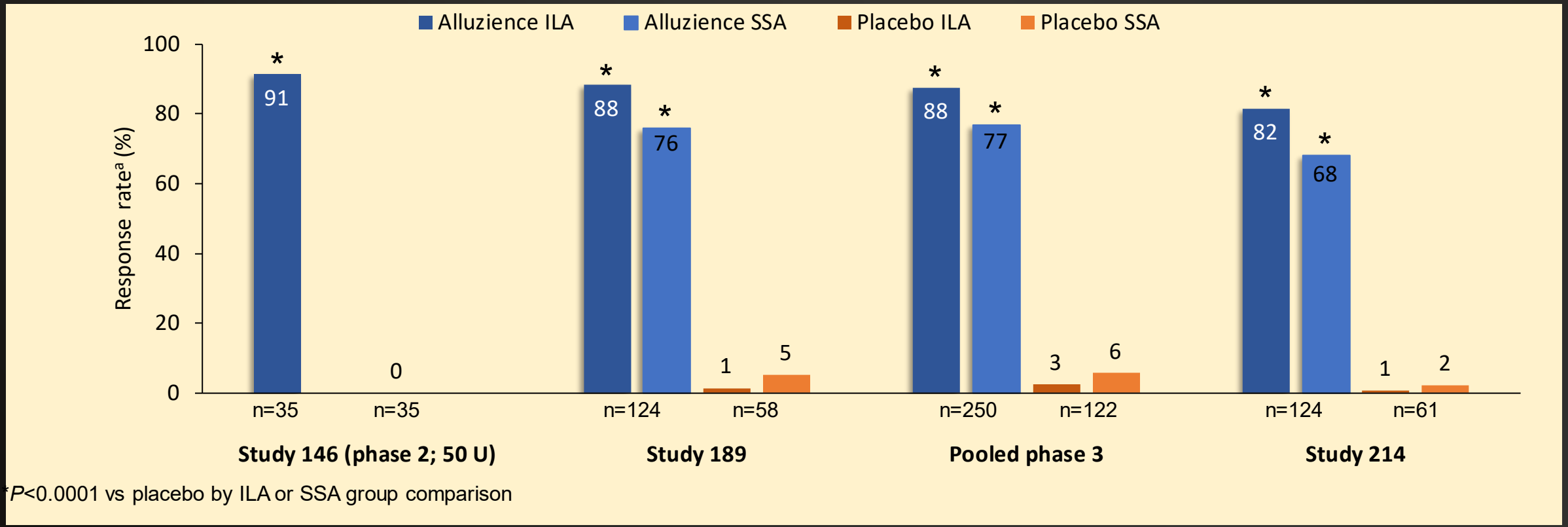
[a]Defined as 'Yes' in response to 'Since being injected have you noticed an improvement in the appearance of your glabellar lines (lines between your eyebrows)?' for the modified intent-to-treat population for pooled studies 189 and 214. Self-assessed using diary card.

1. Alluzience Summary of Product Characteristics 2021; 2. Hilton S, et al. Pooled data from 2 double-blind randomized placebo-controlled phase III studies of ready-to-use toxin for moderate-to-severe glabellar lines. In preparation.

High Efficacy After Single Treatment

delivered high, consistent responses at day 29 across studies by ILA or SSA

'None or Mild' GL Severity at Maximal Frown at Day 29



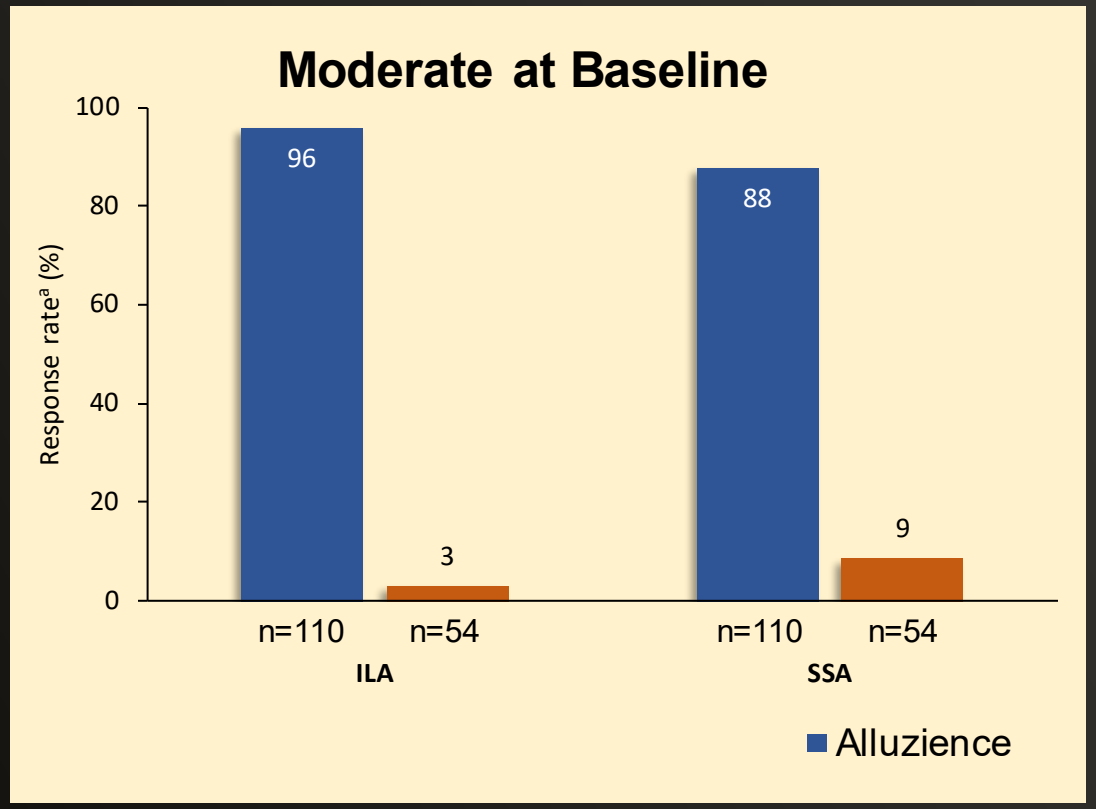
*P<0.0001 vs placebo by ILA or SSA group comparison

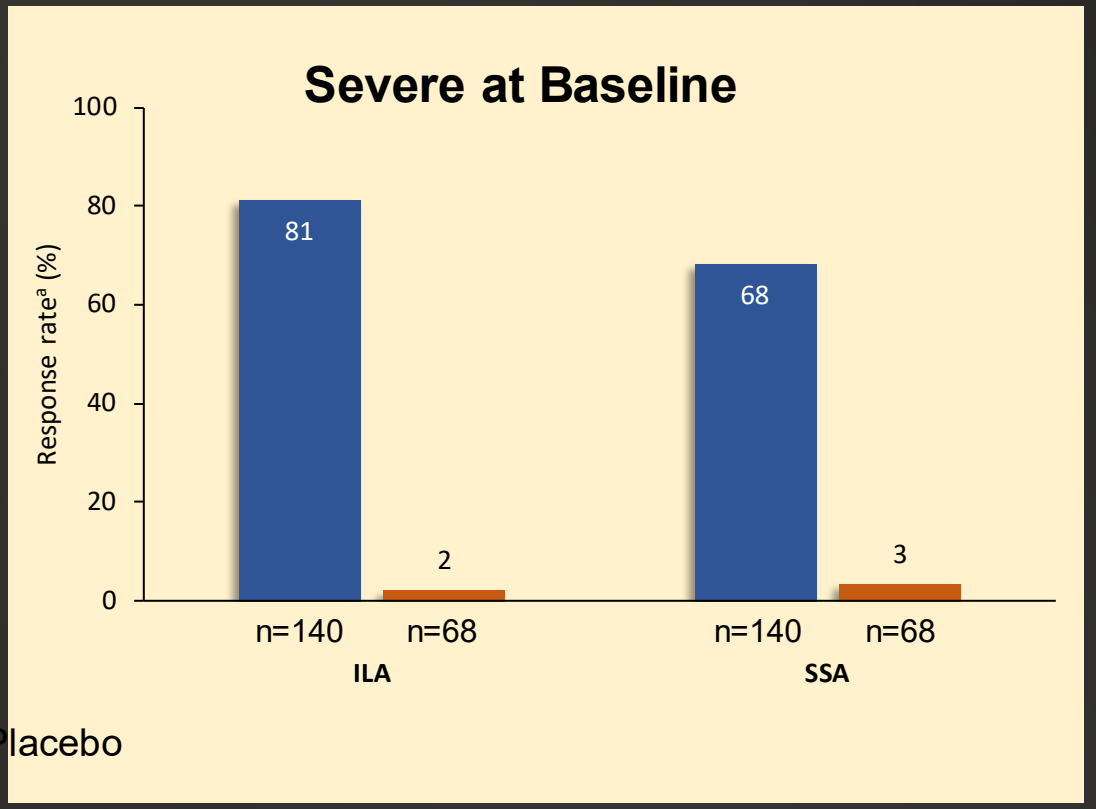
Pooled Phase 3 data from Studies 189 and 214.
GL, glabellar line; ILA, investigator live assessment; SSA, subject self-assessment.
[a]Defined as severity grading of GL as 'none or mild' and calculated based on the modified intent-to-treat population for pooled Studies 189 and 214.

High Efficacy Regardless of Baseline Severity

Response rates were high at day 29 among patients with moderate or severe GL at baseline, as assessed by investigators and subjects

‘None or Mild’ GL Severity at Maximal Frown at Day 29 by Baseline Severity



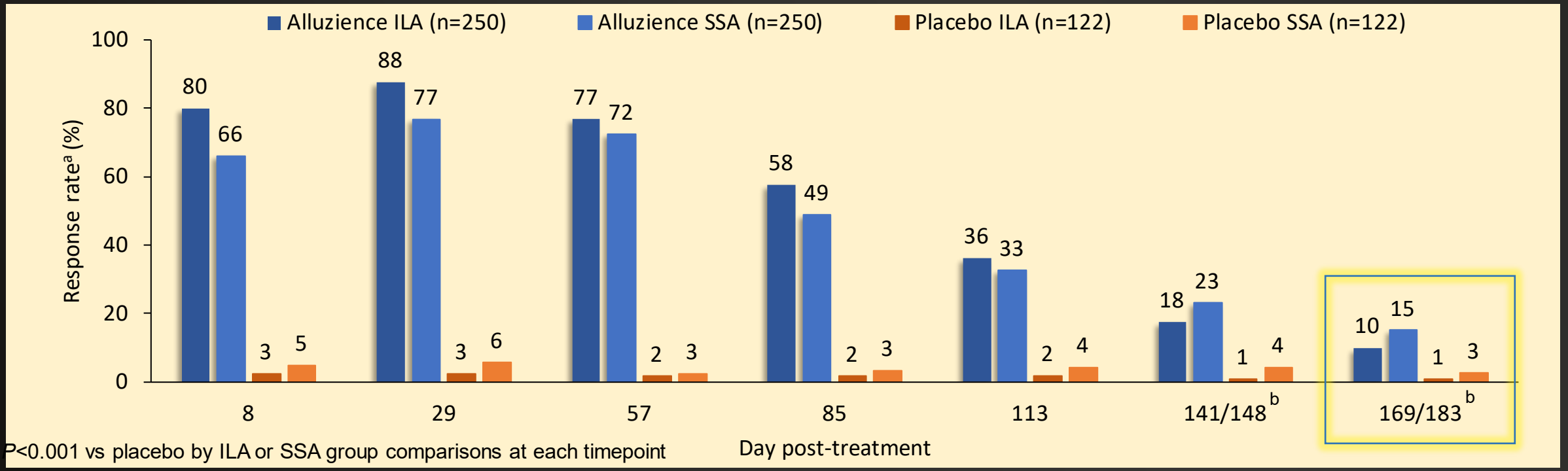


Pooled Phase 3 data from Studies 189 and 214.
GL, glabellar line; ILA, investigator live assessment; SSA, subject self-assessment.
[a]Defined as severity grading of glabellar lines as ‘none or mild.’

Long-Lasting Efficacy: Investigator Assessment

- Responses to Alluzience can last up to 6 months
- At month 6, 10% or 15% of patients had ‘none or mild’ GL severity by ILA or SSA, respectively

‘None or Mild’ GL Severity at Maximal Frown Over Time



Pooled Phase 3 data from Studies 189 and 214.
GL, glabellar line; ILA, investigator live assessment; SSA, subject self-assessment.
[a]Defined as severity grading of glabellar lines as none or mild and calculated based on the modified intent-to-treat population for pooled Studies 189 and 214; [b]Post-treatment assessments on days 148 and 183 correspond to Study 189 and assessments on days 141 and 169 correspond to Study 214.

RelabotulinumtoxinA – Liquid Toxin

Not FDA Approved at This Time

Evaluation of QM1114

Evaluation of QM1114, a novel ready-to-use liquid botulinum toxin, in aesthetic treatment of glabellar lines

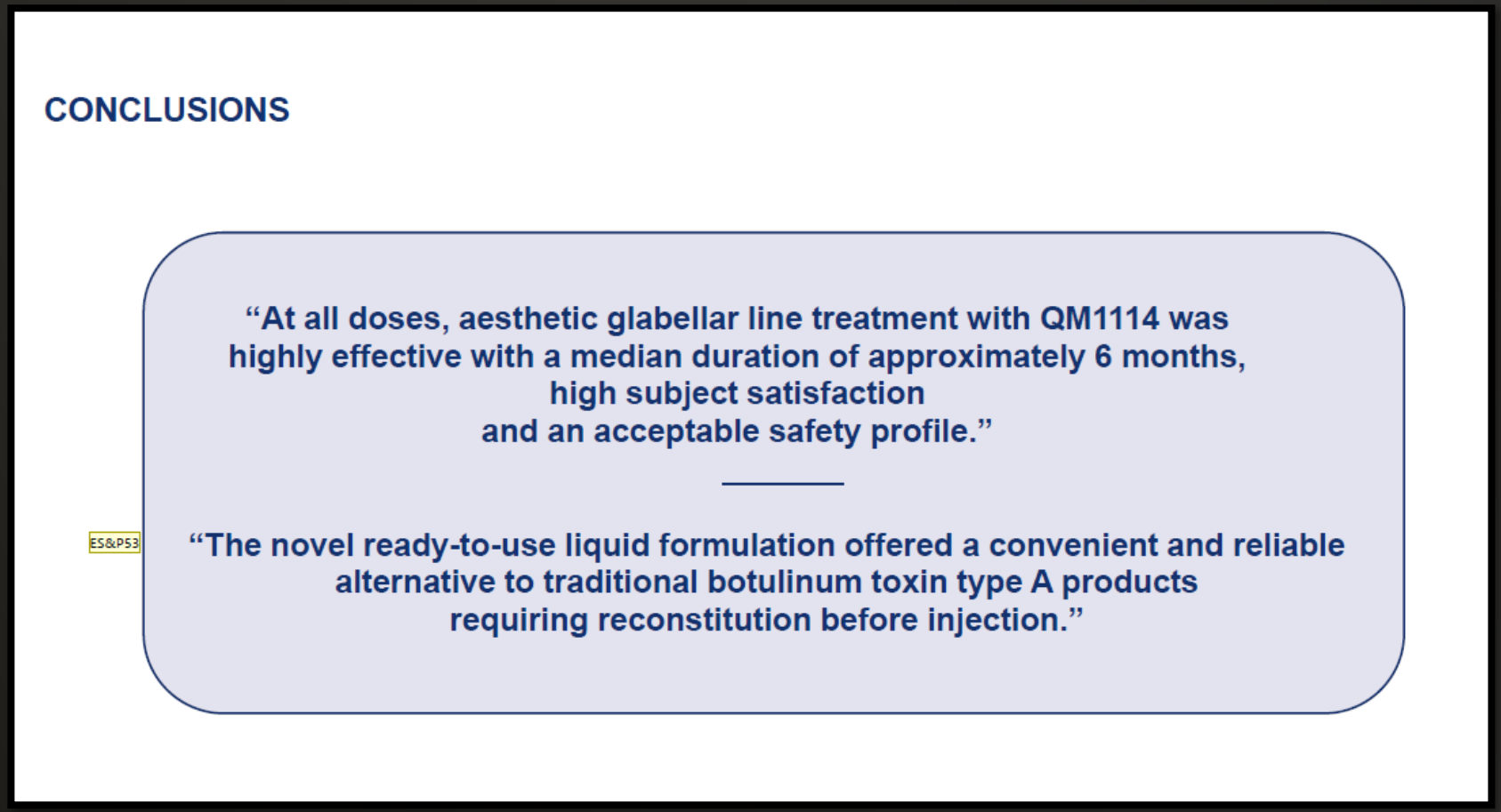
J Cohen, AboutSkin Dermatology and DermSurgery, PC, Englewood, United States
GD Monheit, Total Skin & Beauty Dermatology Center, Birmingham, United States
MS Nestor, Center for Clinical and Cosmetic Research, Aventura, United States
MP Goldman, Cosmetic Laser Dermatology, San Diego, United States
MH Gold, Gold Skin Care Center, Nashville, United States
EH Tichy, Clinical Trials of Texas, Inc., San Antonio, United States
L Swinyer, Dermatology Research Center, Inc., Salt Lake City, United States

Acknowledgement: The authors, together with Dr. F Bodie, Coastal Clinical Research, Inc., Mobile, United States, served as Principal Investigators of the clinical study presented herein.

Medical writing assistance was provided by Carolina Edwartz, PhD, on behalf of Galderma Aesthetics.

Presented at the 24th World Congress of Dermatology, Milan, Italy, 15 June 2019.

Conclusions

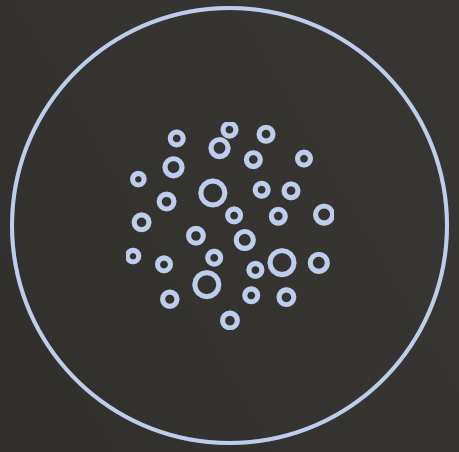


Phase III Clinical Trials in the US now finished – 3 areas studied in these studies – Glabellar Furrows, Crow's Feet, and Forehead Lines – results to be sent to FDA

RelabotulinumtoxinA (RelaBoNT-A): A Novel Ready-to-use Formulation, Botulinum Neurotoxin A1 (BoNT-A1)

RelaBoNT-A is a unique, **ready-to-use liquid formulation** in a saline phosphate buffer solution

RelaBoNT-A is formulated through a modern and gentle manufacturing process **using filtration and chromatography to obtain a clean product** without any precipitations or freeze-drying



It developed from **a proprietary strain of BoNT-A1** and **is highly active** with a specific activity of ~2.0×10^8 U/mg of total protein

RelaBoNT-A is a highly pure (>98%), **complex-free** BoNT-A1 with **no detectable impurities and a neutral pH (6.75)**

RelaBoNT-A is **animal-origin and human-origin free,** with no human- or animal-derived excipients

The highly potent and purified BoNT-A1 formulation eliminates the need for calculation and reconstitution before administration; it was designed for enhanced consistency, performance, and reliability

U, units.

Reference: Sundberg ÅL, Ståhl U. Relabotulinum toxin – a novel, high purity BoNT-A1 in liquid formulation. Poster presented at: TOXINS 2021 Virtual Conference; January 16-17, 2021.

READY Clinical Trial Program

	Pivotal studies			Long-term safety
	READY-1	**READY-2**	**READY-3**	**READY-4**
Treatment & Design	Glabellar lines (GL)	Lateral canthal lines (LCL)	GL + LCL alone or in combination	GL + LCL
	Single treatment			Up to 4 treatments, ≥12 weeks apart
	Randomized, double-blind, placebo-controlled, parallel group, 6-month follow-up			Open-label, repeat treatment, up to 12 months' follow-up
Subjects	10 sites (US & Canada)	10 sites (US & Canada)	12 sites (US & Canada)	30 sites (US)
	Men and women, 18 years or older, with moderate-to-severe lines at maximum frown for GL / maximum smile for LCL			
Assessments	**Efficacy** • Line severity, 4-point scales, assessed by investigators and subjects • Onset of effect: subject diary card • Aesthetic improvement: 7-graded Global Aesthetic Improvement Scale (GAIS) • FACE-Q psychological function • Subject satisfaction			**Efficacy** • Line severity • GAIS
	Safety • Adverse events, neutralizing antibodies			
	PRIMARY ENDPOINT: Month-1 composite response of none-or-mild line severity and ≥2-grade improvement, assessed by both investigators and subjects concurrently			**PRIMARY OBJECTIVE:** Safety
Randomized Subjects	300 RelaBoNT-A: 225 Placebo: 75	303 RelaBoNT-A: 230 Placebo: 73	413 GL relaBoNT-A/LCL placebo: 121 LCL relaBoNT-A/GL placebo: 118 GL + LCL relaBoNT-A: 115 GL + LCL placebo: 59	902 All subjects received relaBoNT-A
Registration on clinicaltrials.gov	NCT04249583	NCT04249687	NCT04247074	NCT04225260

GL, glabellar lines; ILA, investigator live assessment; ITT, intent-to-treat; LCL, lateral canthal lines; READY, RElabotulinumtoxin Aesthetic Development studY; SLA, subject live assessment; TEAE, treatment-emergent adverse event.

A Multicenter, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of RelabotulinumtoxinA

(QM1114) for the Treatment of Moderate-to-Severe Glabellar Lines (READY-1)

READY-1 data based on 43QM1602 Clinical Study Report.

READY-1 Primary Objective

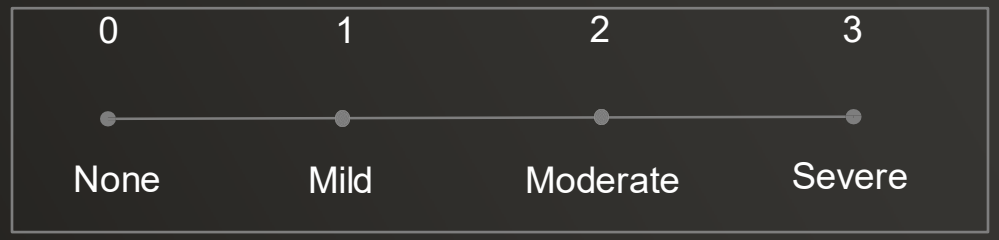
Primary Objective

- The primary objective of READY-1 was to evaluate a single dose of 50 U relaBoNT-A compared to placebo for the treatment of moderate-to-severe GL

Primary Endpoint

- The primary endpoint was the composite 2-grade responder rate evaluated using the GL Investigator Live Assessment (GL-ILA) 4-Point Photographic Scale and GL Subject Live Assessment (GL-SLA) Static 4-Point Categorial Scale at maximum frown at Month 1
- A composite 2-grade responder was defined as a subject who achieved both a score of none (0) or mild (1) in GL severity and had at least a 2-grade improvement from baseline on both the GL-ILA 4-Point Photographic Scale of GL severity and GL-SLA Static 4-Point Categorical Scale

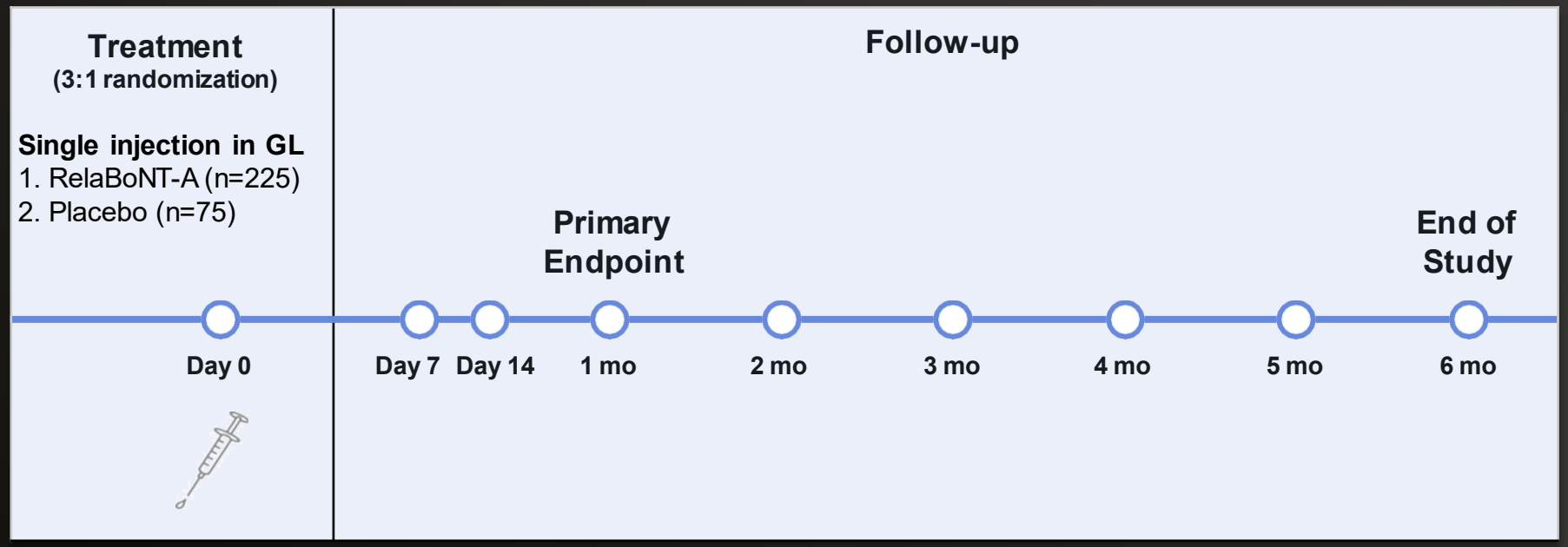
GL-ILA 4-Point Scale



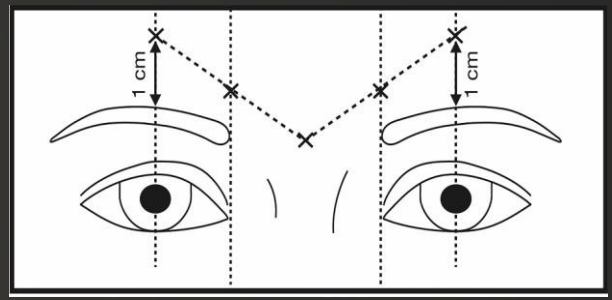
GL, glabellar lines; ILA, investigator live assessment; READY, RElabotulinumtoxin Aesthetic Development studY; SLA, subject live assessment; U, units.

READY-1 Study Design

Phase 3, multicenter, randomized, parallel-group, double-blind, placebo-controlled trial in 300 subjects with moderate-to-severe glabellar lines (GL) across 10 sites (US and Canada)



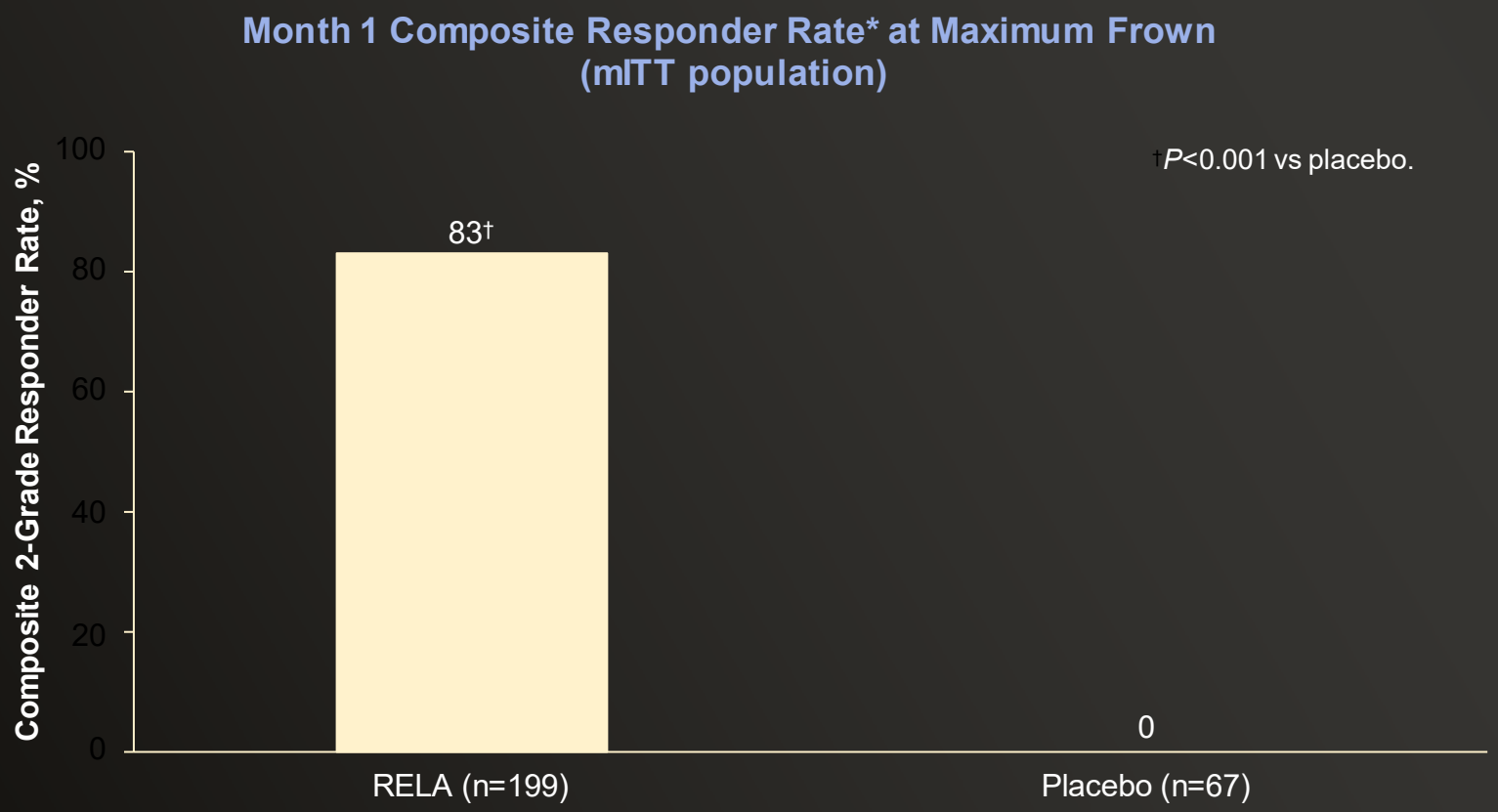
Injection Pattern for GL Treatment



10 U (0.1 mL) of relaBoNT-A was injected into each of 5 injection sites for a total dose of 50 U (0.5 mL)

GL, glabellar lines; mo, month; READY, RElabotulinumtoxin Aesthetic Development studY; U, units.

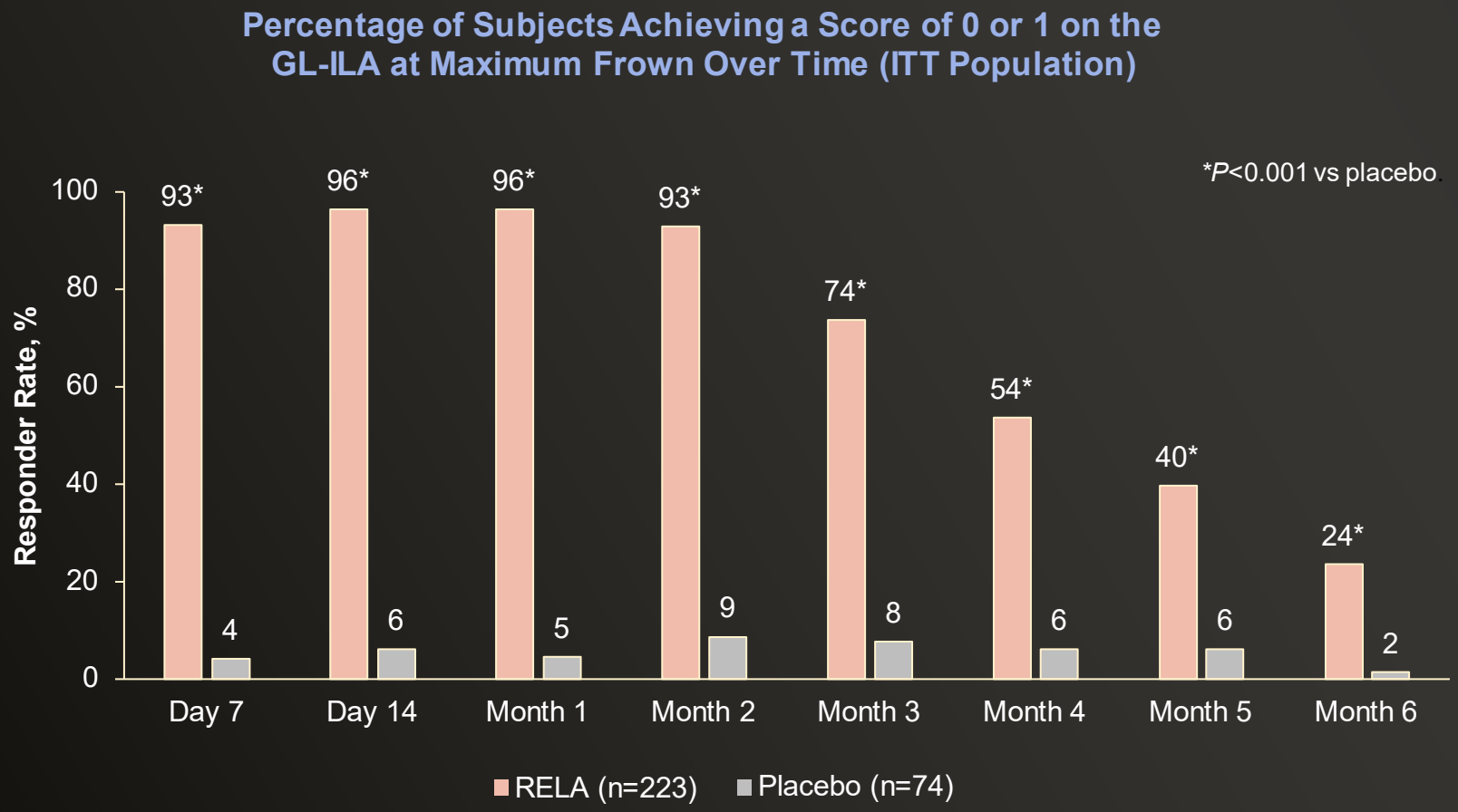
Primary Endpoint: Month 1 Composite 2-Grade Responder Rate at Maximum Frown



READY-1 **met its primary endpoint**

*A composite 2-grade responder was defined as a subject who achieved both a score of none (0) or mild (1) in GL severity and had at least a 2-grade improvement from baseline on both the GL-ILA 4-Point Photographic Scale of GL severity and GL-SLA Static 4-Point Categorical Scale at maximum frown.
GL, glabellar lines; ILA, investigator live assessment; mITT, modified intent-to-treat; READY, RElabotulinumtoxin Aesthetic Development studY; RELA, relaBoNT-A; SLA, subject live assessment.

Secondary Endpoint: GL-ILA Responder Rates at Maximum Frown Over Time

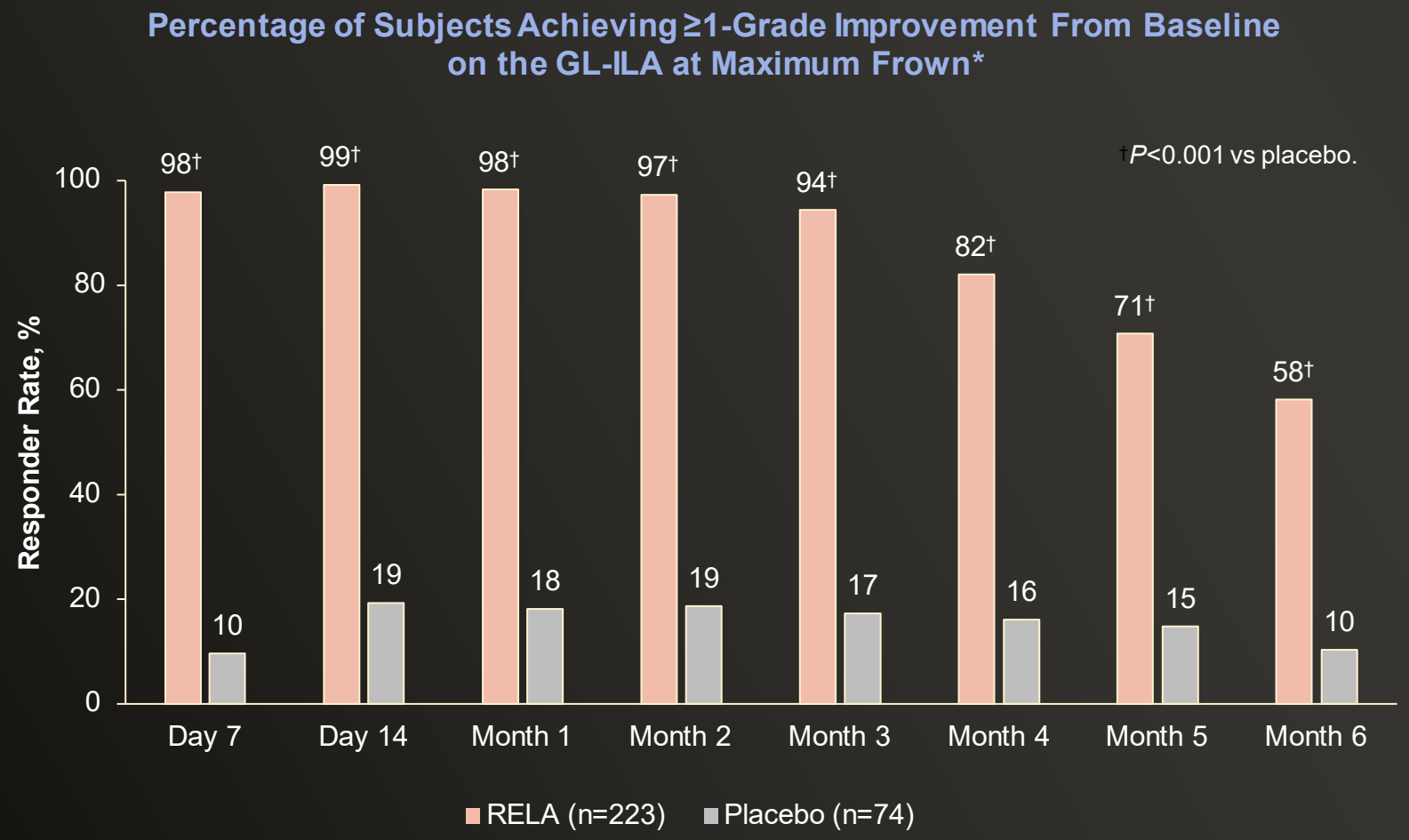


Significantly more subjects treated with relaBoNT-A **achieved a score of 0 or 1 on the GL-ILA at every time point** compared with placebo (*P*<0.001)

At **Month 1, 96% of subjects** treated with relaBonT-A achieved a score of 0 or 1, with **24% maintaining this score at Month 6**

GL, glabellar lines; ILA, investigator live assessment; ITT, intent-to-treat; RELA, relaBoNT-A.

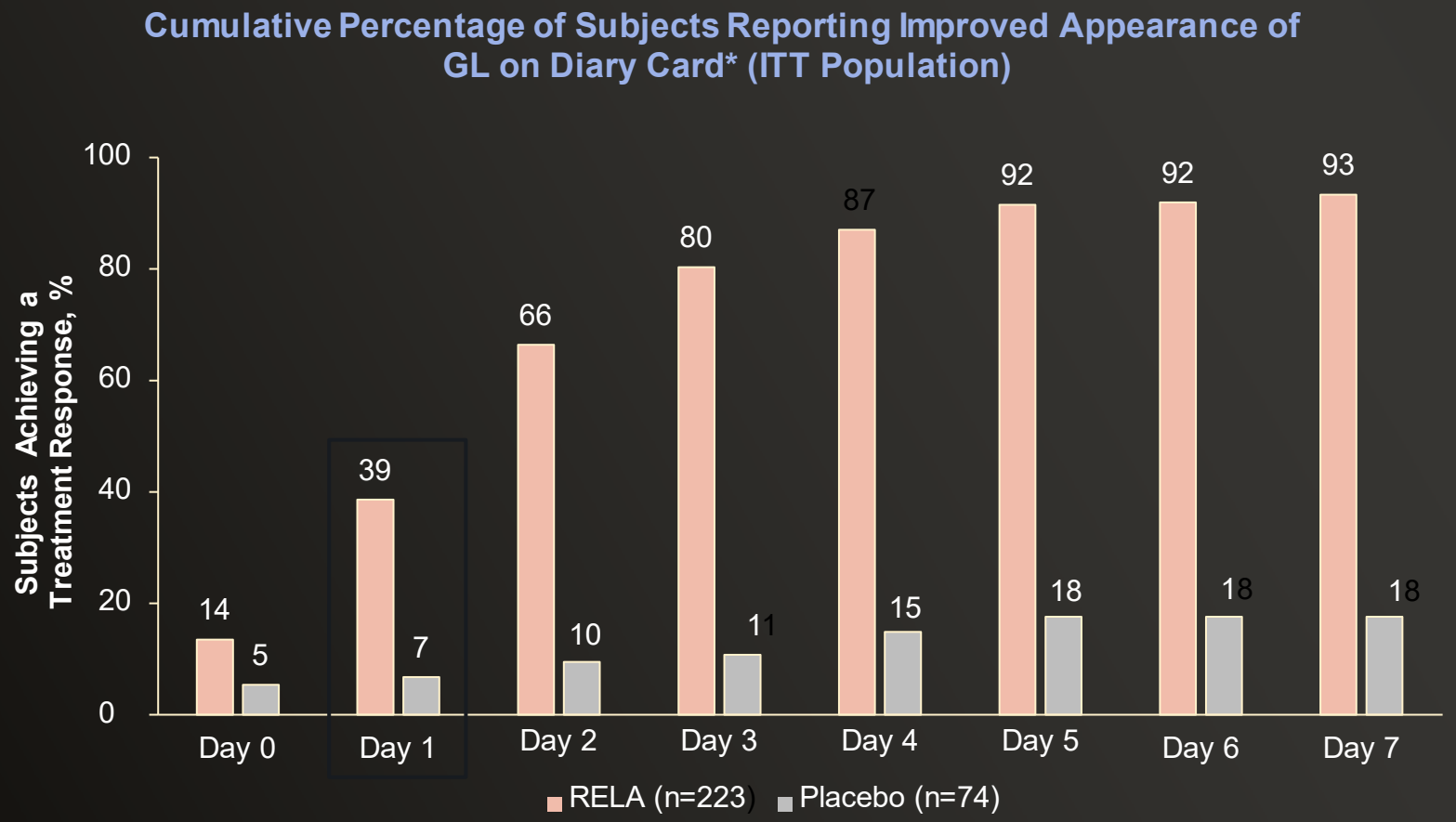
GL-ILA at Maximum Frown: ≥1-Grade Improvement



98% of subjects treated with relaBoNT-A had ≥1-grade improvement at Month 1, with **58%** of subjects maintaining improvement through Month 6 (*P*<0.001 vs placebo)

*Exploratory endpoint. Subjects were from the ITT population.
GL, glabellar lines; ITT, intent-to-treat; RELA, relaBoNT-A.

Time to Onset of Effect Based on Diary Card

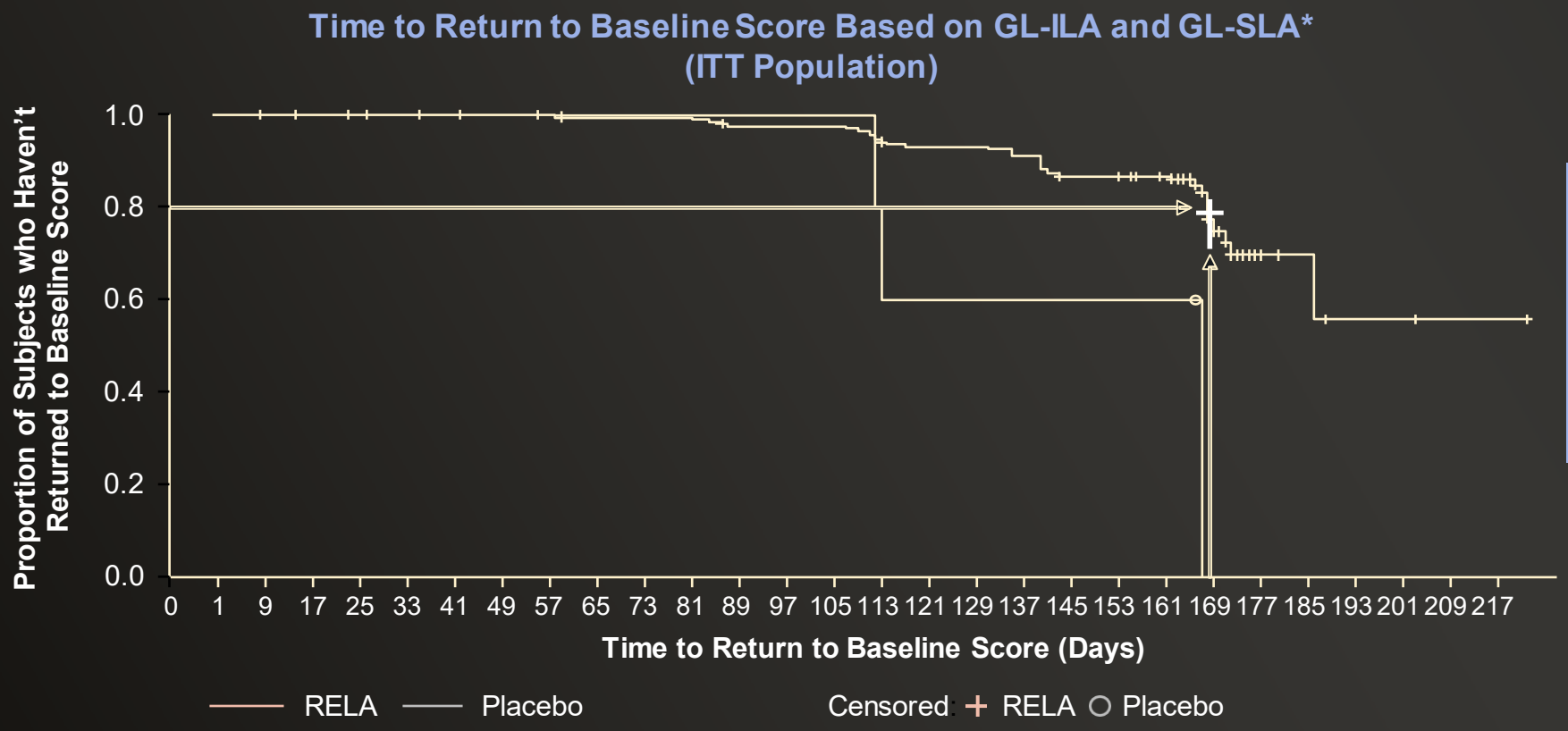


The median time to onset of GL improvement with relaBoNT-A treatment was **2 days**

39% of subjects treated with relaBoNT-A reported onset of effect by Day 1

*Exploratory endpoint. Subjects were asked to record a "yes" or "no" answer in a diary card each day on Days 0 through 7 to the question, "Since being injected, have you noticed an improvement in the appearance of your glabellar lines (lines between your eyebrows) when you frown?"
GL, glabellar lines; ITT, intent-to-treat; RELA, relaBoNT-A.

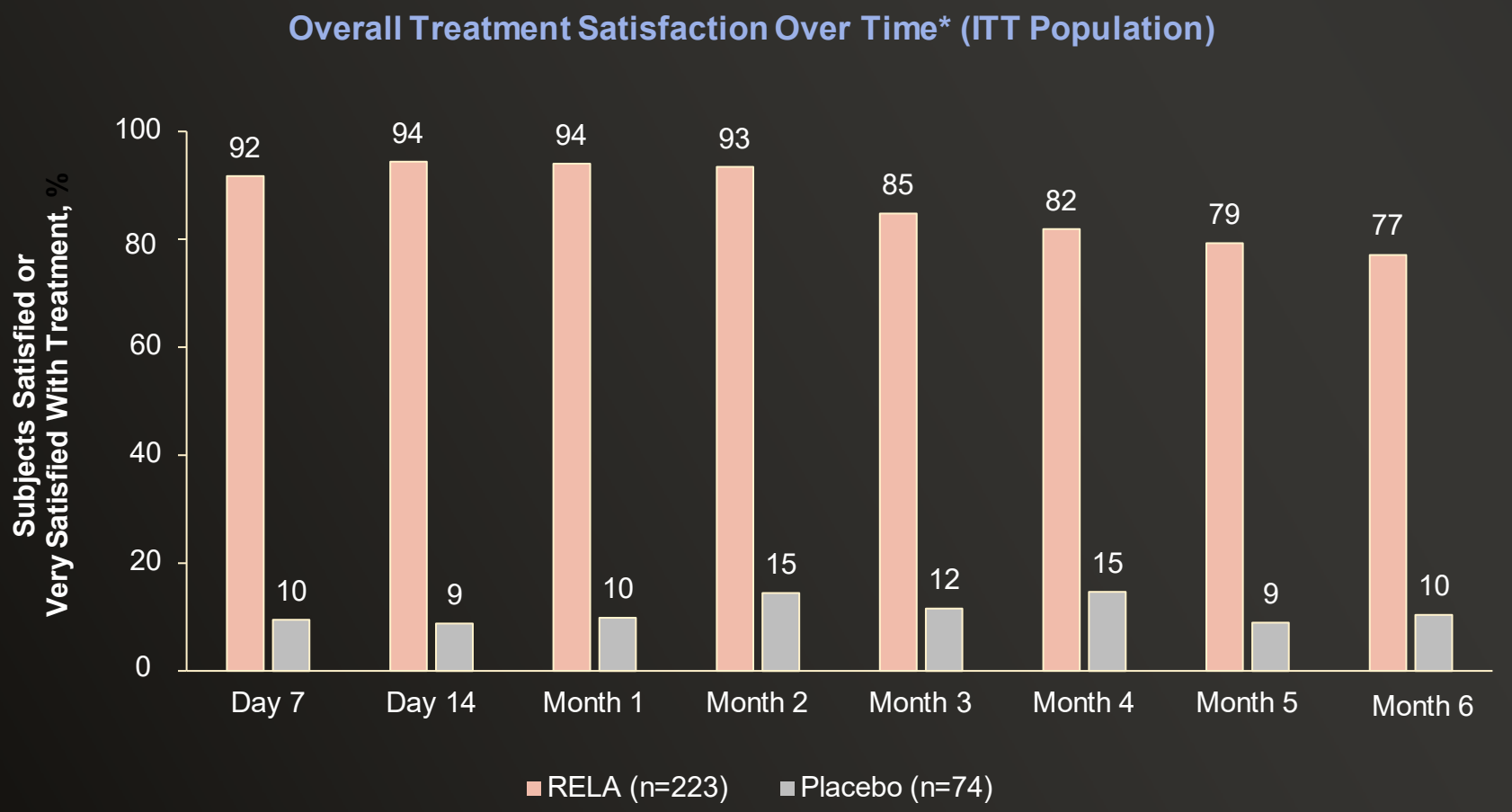
Time to Return to Baseline on Both GL-ILA and GL-SLA



†**Approximately 80%** of subjects did not return to baseline within 24 weeks of relaBoNT-A treatment

*Exploratory endpoint. Time to return to baseline was assessed in subjects who achieved a score of 0 or 1 on both the GL-ILA 4-Point Photographic Scale and GL-SLA Static 4-Point Categorical Scale at maximum frown. †Arrows point to the approximate percentage of subjects treated with relaBoNT-A who had not returned to baseline at 24 weeks (168 days).
GL, glabellar lines; ILA, investigator live assessment; ITT, intent-to-treat; RELA, relaBoNT-A; SLA, subject live assessment.

Overall Treatment Satisfaction on FLTSQ



At Month 1, **94%** of subjects treated with relaBoNT-A were satisfied with treatment and **77%** remained satisfied through Month 6

*Exploratory endpoint. Patients were instructed to report whether they were "very dissatisfied," "dissatisfied," "neither satisfied nor dissatisfied," "satisfied," or "very satisfied" with their treatment on the FLTSQ when asked "How would you describe your satisfaction with your treatment now?"

FLTSQ, Facial Lines Treatment Satisfaction Questionnaire; ITT, intent-to-treat; RELA, relaBoNT-A.

A Multicenter, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of RelabotulinumtoxinA

(QM1114) for the Treatment of Moderate-to-Severe Lateral Canthal Lines (READY-2)

READY-2 data based on 43QM1901 Clinical Study Report.

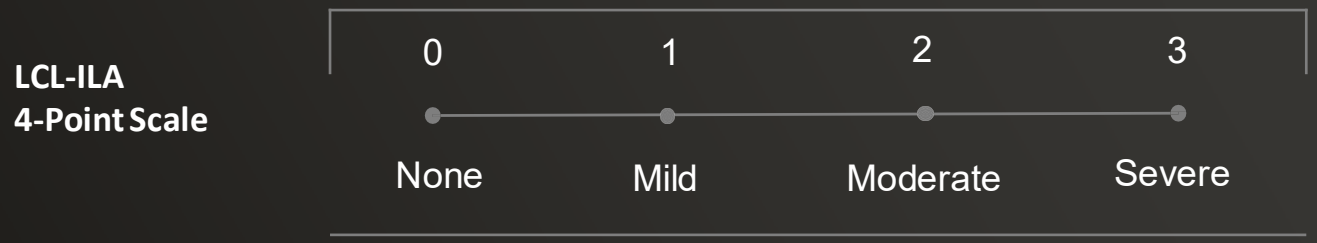
READY-2 Primary Objective

Primary Objective

- The primary objective of READY-2 was to evaluate a single dose of 60 U relaBoNT-A compared with placebo for the treatment of moderate-to-severe LCL

Primary Endpoint

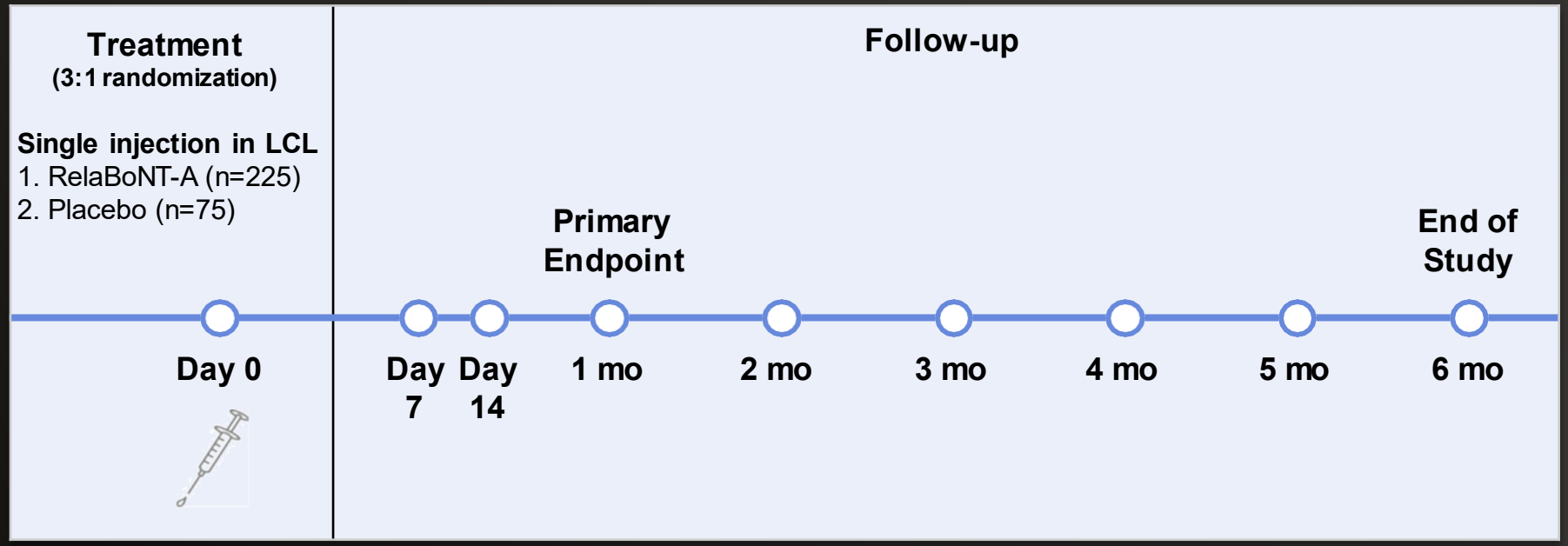
- The primary endpoint was the composite 2-grade responder rate evaluated using the LCL Investigator Live Assessment (LCL-ILA) 4-Point Photographic Scale and LCL Subject Live Assessment (LCL-SLA) 4-Point Photographic Scale at maximum smile at Month 1
- A composite 2-grade responder was defined as a subject who achieved both a score of none (0) or mild (1) in LCL severity and had at least a 2-grade improvement from baseline on both the LCL-ILA 4-Point Photographic Scale of LCL Severity and LCL-SLA 4-Point Photographic Scale



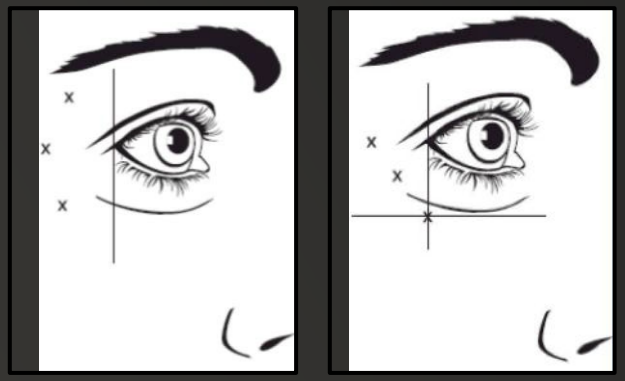
ILA, investigator live assessment; LCL, lateral canthal lines; READY, RElabotulinumtoxin Aesthetic Development studY; SLA, subject live assessment; U, units.

READY-2 Study Design

Phase 3, multicenter, randomized, parallel-group, double-blind, placebo-controlled trial in 300 subjects with moderate-to-severe LCL across 10 sites (US and Canada)



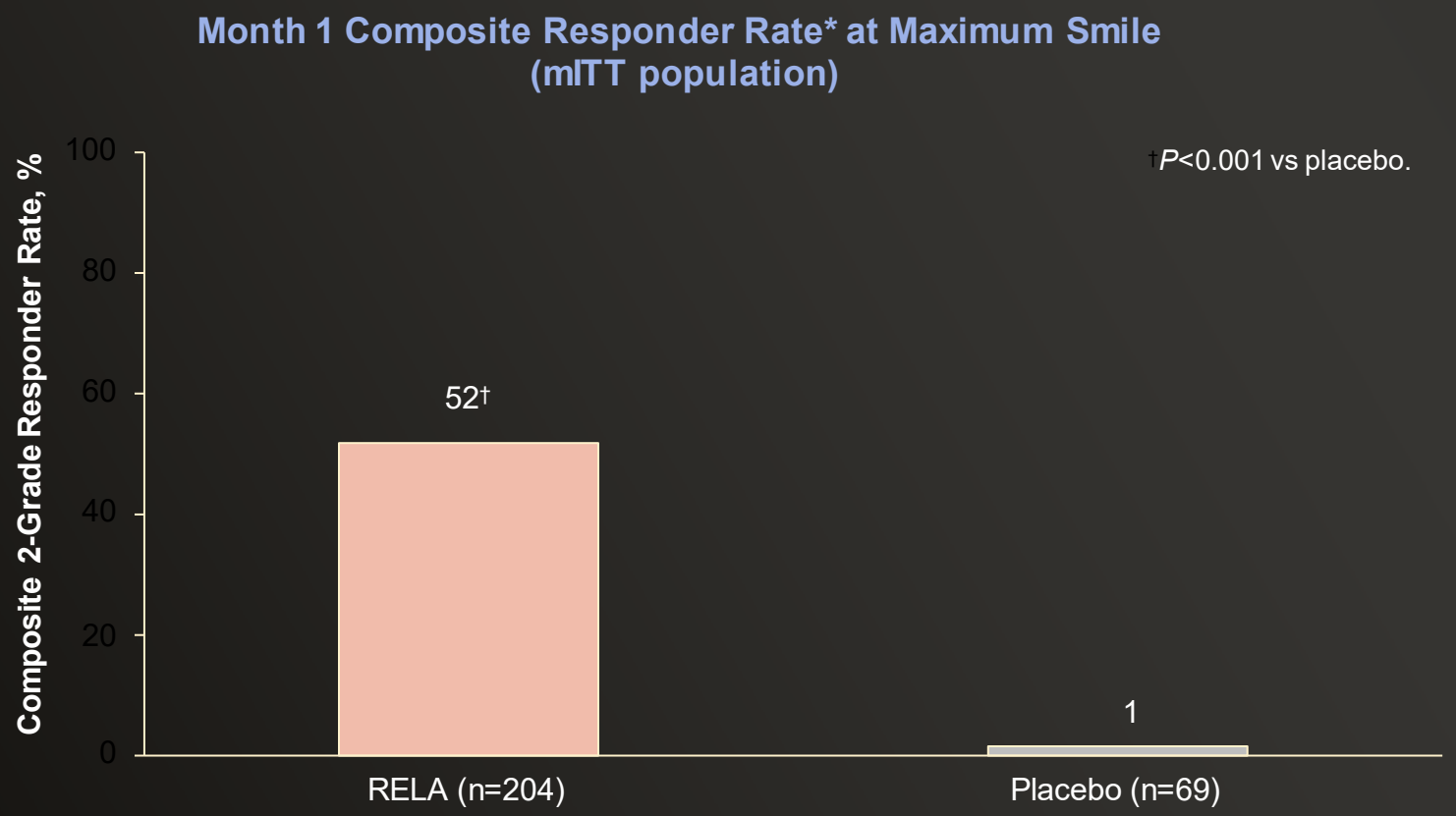
Two Injection Options for LCL Treatment



10 U (0.1 mL) of relaBoNT-A was injected into each of 6 injection sites for a total dosage of 60 U (0.6 mL)

LCL, lateral canthal lines; mo, month; READY, RElabotulinumtoxin Aesthetic Development studY; U, units.

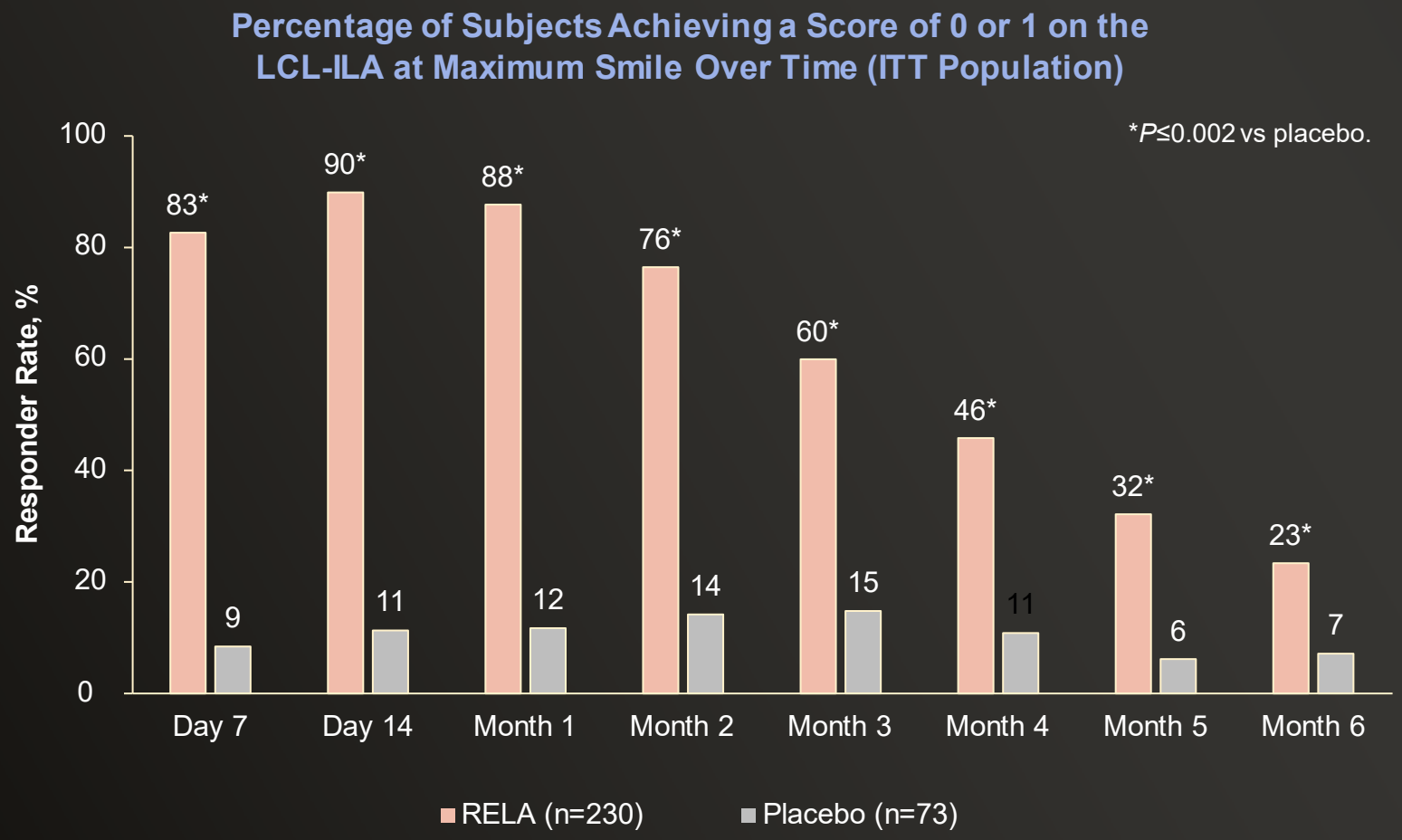
Primary Endpoint: Month 1 Composite 2-Grade Responder Rate at Maximum Smile



READY-2 **met its primary endpoint**

*A composite 2-grade responder was defined as a subject who achieved both a score of none (0) or mild (1) in LCL severity and had at least a 2-grade improvement from baseline on both the LCL-ILA 4-Point Photographic Scale of LCL severity and LCL-SLA 4-Point Photographic Scale at maximum smile.
ILA, investigator live assessment; LCL, lateral canthal lines; mITT, modified intent-to-treat; READY, REIabotulinumtoxin Aesthetic Development studY; RELA, relaBoNT-A; SLA, subject live assessment.

Secondary Endpoint: LCL-ILA Responder Rates at Maximum Smile Over Time

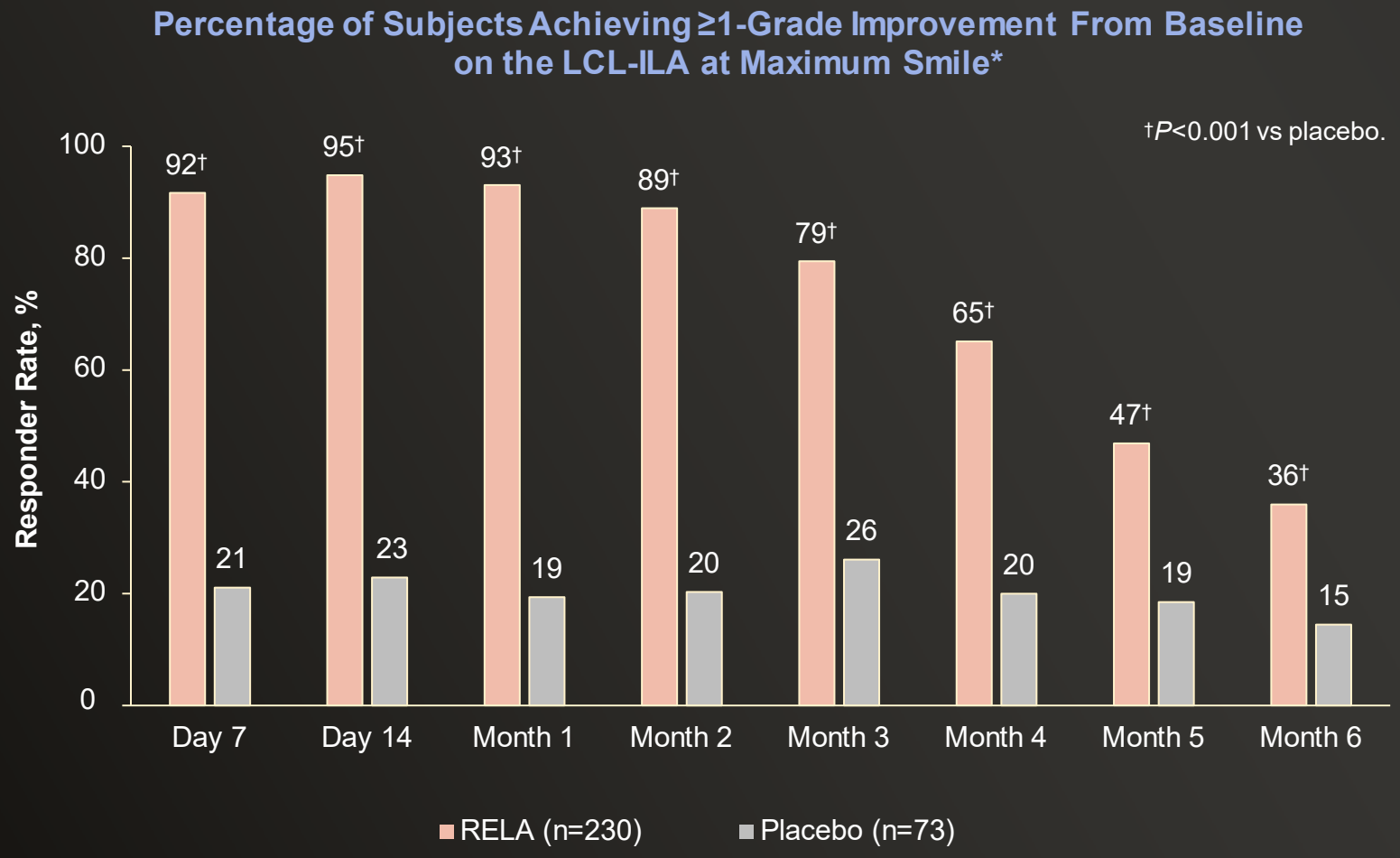


Significantly more subjects treated with relaBoNT-A **achieved a score of 0 or 1 on the LCL-ILA at every timepoint** compared with placebo (*P*≤0.002)

At **Month 1, 88% of subjects** treated with relaBoNT-A achieved a score of 0 or 1, with **23% maintaining this score at Month 6**

ILA, investigator live assessment; ITT, intent-to-treat; LCL, lateral canthal lines; RELA, relaBoNT-A

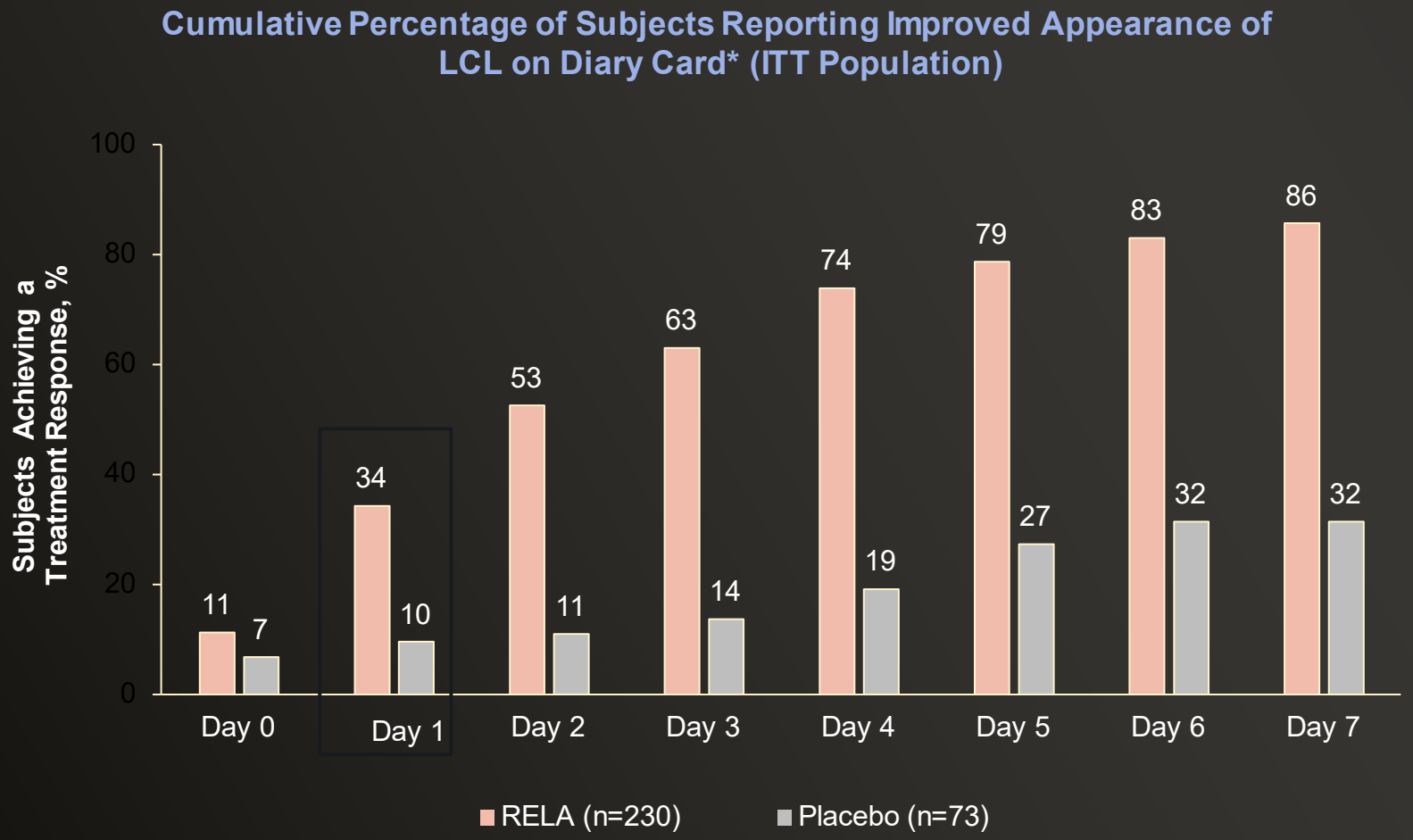
LCL-ILA at Maximum Smile: ≥1-Grade Improvement



93% of subjects treated with relaBoNT-A had ≥1-grade improvement at Month 1, with **36%** of subjects maintaining improvement through Month 6 (*P*<0.001 vs placebo)

*Exploratory endpoint. Subjects were from the ITT population.
ILA, investigator live assessment; ITT, intent-to-treat; LCL, lateral canthal lines; RELA, relaBoNT-A

Time to Onset of Effect Based on Diary Card

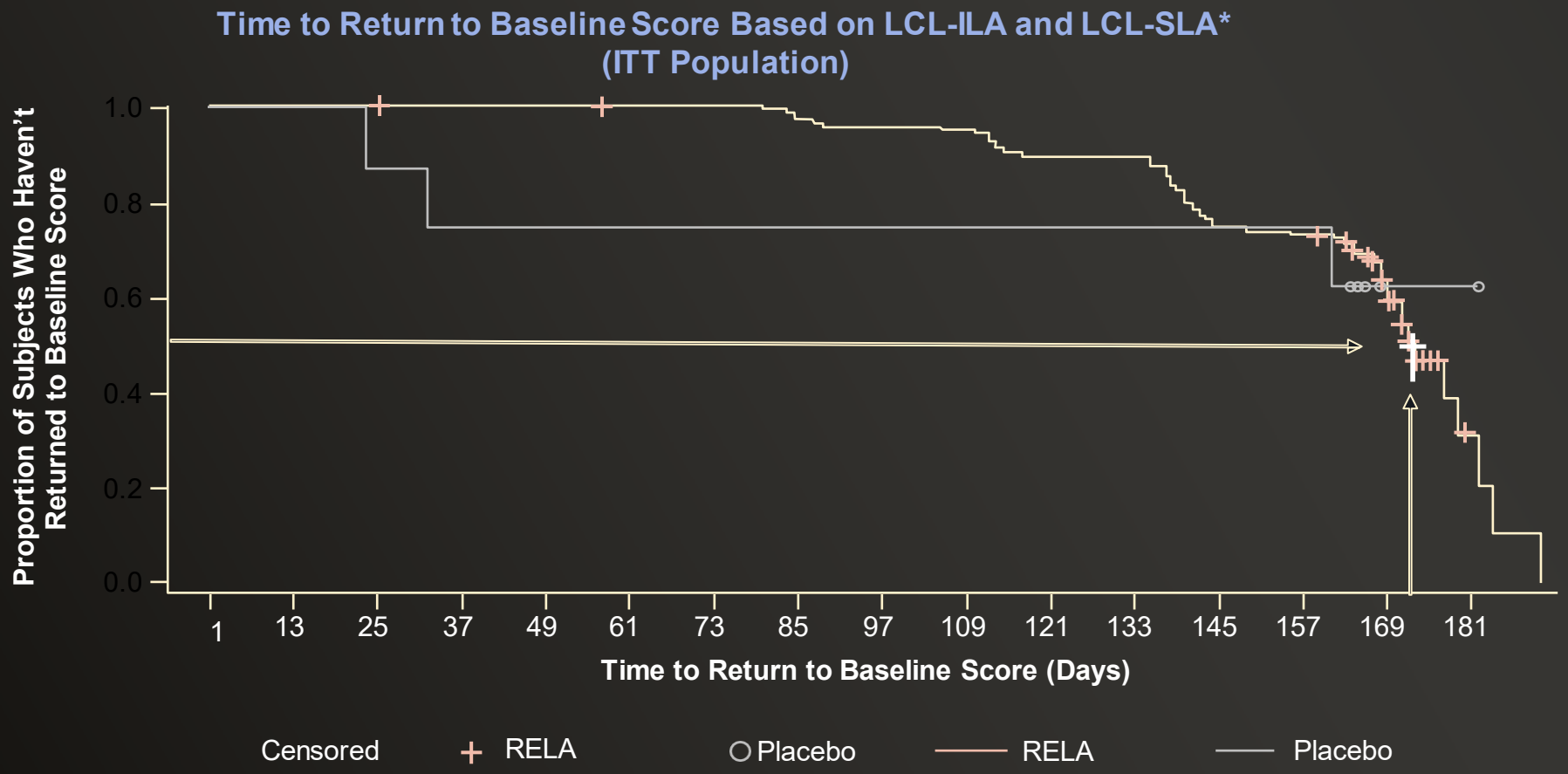


The median time to onset of LCL improvement with relaBoNT-A treatment was **2 days**

34% of subjects treated with relaBoNT-A reported onset of effect by Day 1

*Exploratory endpoint. Subjects were asked to record a "yes" or "no" answer in a diary card each day on Days 0 through 7 to the question, "Since being injected, have you noticed an improvement in the appearance of your lateral canthal lines (crow's feet) when you smile?"
ITT, intent-to-treat; LCL, lateral canthal lines; RELA, relaBoNT-A.

Time to Return to Baseline on Both LCL-ILA and LCL-SLA

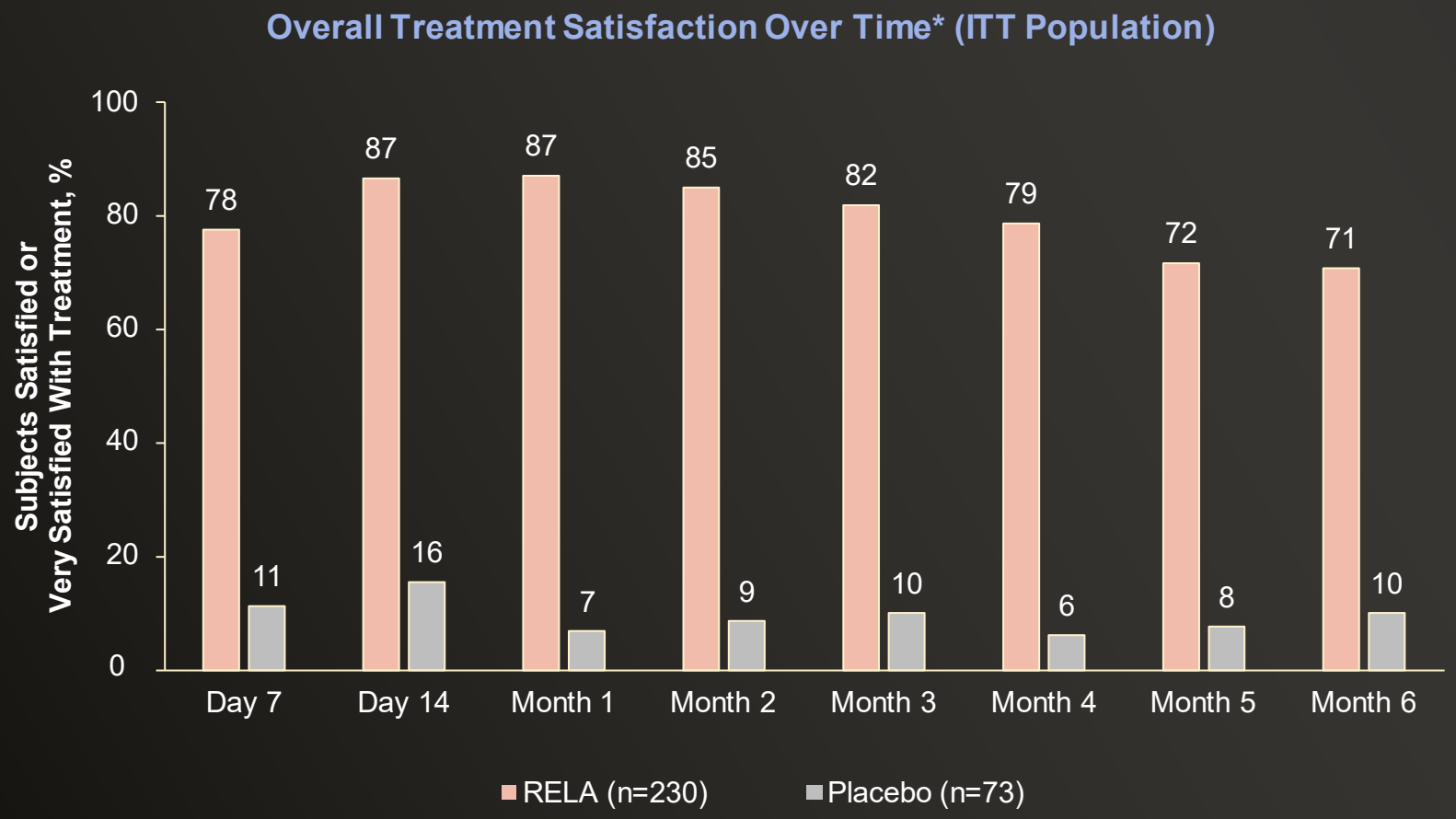


†**Approximately 60%** of subjects did not return to baseline within 24 weeks of relaBoNT-A treatment

The median time to return to baseline was **24.7 weeks** (173 days) after relaBoNT-A treatment

*Exploratory endpoint. Time to return to baseline was assessed in subjects who achieved a score of 0 or 1 on both the LCL-ILA 4-Point Photographic Scale and LCL-SLA 4-Point Photographic Scale at maximum smile. †Arrows point to the approximate percentage of subjects treated with relaBoNT-A who had not returned to baseline at 24 weeks (168 days).
ILA, investigator live assessment; ITT, intent-to-treat; LCL, lateral canthal lines; RELA, relaBoNT-A; SLA, subject live assessment.

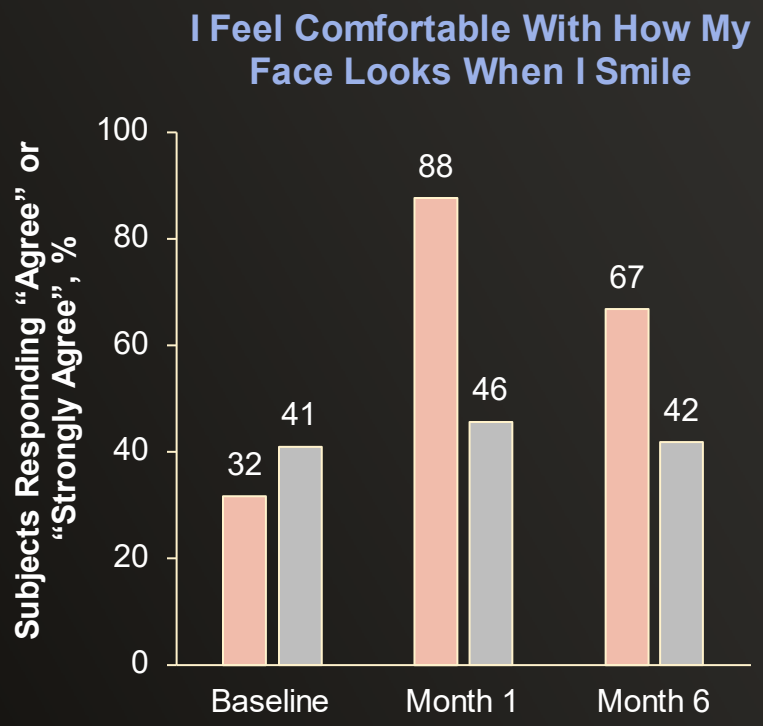
Overall Treatment Satisfaction on FLTSQ

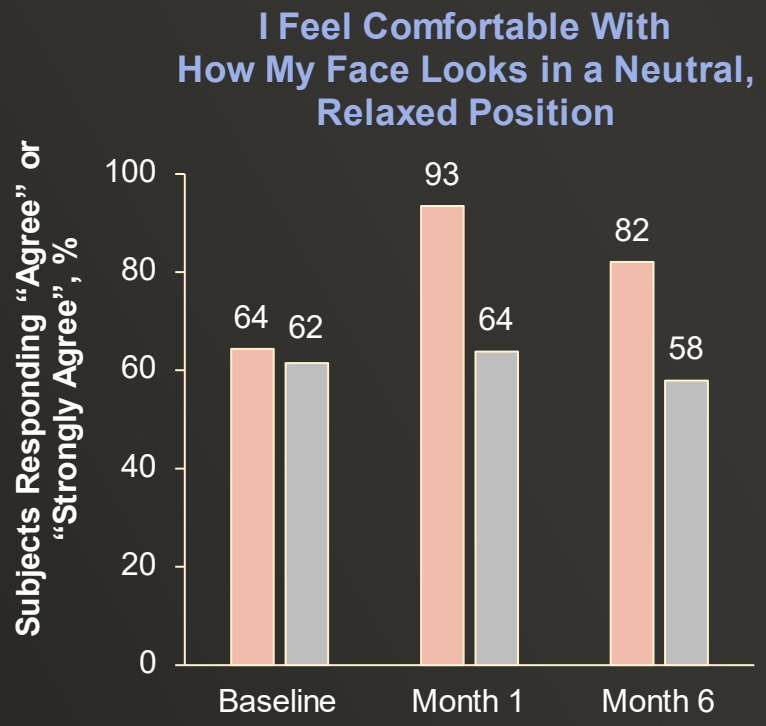


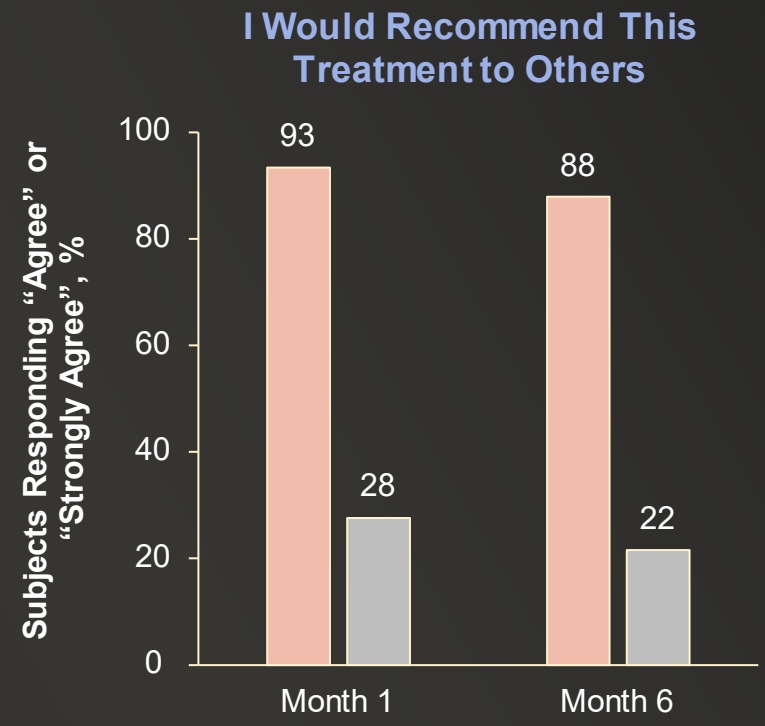
At Month 1, **87%** of subjects treated with relaBoNT-A were satisfied with treatment and **71%** remained satisfied through Month 6

*Exploratory endpoint. Patients were instructed to report whether they were "very dissatisfied," "dissatisfied," "neither satisfied nor dissatisfied," "satisfied," or "very satisfied" with their treatment on the FLTSQ when asked "How would you describe your satisfaction with your treatment now?"
FLTSQ, Facial Lines Treatment Satisfaction Questionnaire; ITT, intent-to-treat; RELA, relaBoNT-A.

Subjects Reported Feeling Comfortable With Facial Appearance and Would Recommend RelaBoNT-A Treatment on FLTSQ*







*Exploratory endpoint. Subjects in the ITT population responded with "agree" or "strongly agree" to the statements "I feel comfortable with how my face looks when I smile," "I feel comfortable with how my face looks in a neutral, relaxed position," and "I would recommend this treatment to others" on the FLTSQ.
FLTSQ, Facial Lines Treatment Satisfaction Questionnaire; ITT, intent-to-treat; RELA, relaBoNT-A.

Incidence of TEAEs

Brief Summary of TEAEs in Safety Population, n (%)	RELA (n=230)	Placebo (n=73)
Subjects with at least 1 TEAE	60 (26)	18 (25)
Subjects with at least 1 SAE	3 (1)	1 (1)
Subjects with SAE related to product and/or injection procedure	0	0
TEAE leading to discontinuation	0	0
Treatment-related TEAEs		
Subjects with at least 1 treatment-related TEAE	14 (6)	4 (6)
General disorders and administration-site conditions	12 (5)	4 (6)
• Injection-site bruising*	11 (5)	3 (4)
• Injection-site pain*	1 (0)	1 (1)
Nervous system disorders	1 (0)	1 (1)
• Headache*	1 (0)	1 (1)
Musculoskeletal and connective tissue disorders	1 (0)	0
• Muscular weakness*	1 (0)	0

*Treatment-related TEAEs were mild or moderate in intensity and resolved during the study.
RELA, relaBoNT-A; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

READY-2 Met Its Primary Endpoint With a Fast Onset and Long Duration in LCL

- In READY-2, significantly more subjects treated with relaBoNT-A were LCL composite 2-grade responders* at Month 1 vs placebo (52% vs 1%, respectively; *P*<0.001)

- RelaBoNT-A demonstrated a fast onset of effect in LCL
  - Within 1 day of relaBoNT-A treatment, 34% of subjects reported an improvement in LCL, and the median time to onset of improvement was 2 days

- Duration of effect of relaBoNT-A in LCL was approximately 6 months (24 weeks) for the majority of subjects
  - Approximately 60% of subjects treated with relaBoNT-A did not return to baseline within 24 weeks
  - At Month 1, 93% of subjects treated with relaBoNT-A achieved a ≥1 grade improvement from baseline on LCL-ILA at maximum smile, with 36% of patients maintaining response at Month 6

*A composite 2-grade responder was defined as a subject who achieved both a score of none (0) or mild (1) in LCL severity and had at least a 2-grade improvement from baseline on both the LCL-ILA 4-Point Photographic Scale of LCL severity and LCL-SLA 4-Point Photographic Scale at maximum smile.
ILA, investigator live assessment; LCL, lateral canthal lines; READY, REIabotulinumtoxin Aesthetic Development studY; SLA, subject live assessment.

READY-2 Results Showed High Subject Satisfaction and a Favorable Risk-Benefit Profile in LCL

- More than 85% of subjects at Month 1 and >65% at Month 6 were satisfied with relaBoNT-A treatment for LCL and how natural they looked according to FLTSQ and the Natural Expressions Questionnaire
  - 93% of subjects rated themselves as improved at maximum smile on the GAIS at Month 1
  - Mean FACE-Q™ Psychological Function total score was 85 at Month 1 compared with 71 at baseline

- Safety data show that relaBoNT-A has a favorable risk-benefit profile in LCL
  - Treatment-related TEAEs were mild or moderate in intensity and resolved during the study
  - The most common treatment-related TEAEs were injection-site bruising (5%), injection-site pain (0%), headache (0%), and muscular weakness (0%)

FLTSQ, Facial Lines Treatment Satisfaction Questionnaire; GAIS, Global Aesthetic Improvement Scale; LCL, lateral canthal lines; READY, REIabotulinumtoxin Aesthetic Development studY; TEAE, treatment-emergent adverse event.

NivobotulinumtoxinA– Liquid Toxin

Not FDA Approved at This Time

To Be developed by Luvantas

The Efficacy and Safety of Liquid-Type Botulinum Toxin Type A for the Management of Moderate to Severe Glabellar Frown Lines
Plast Reconstr Surg. 2015 Mar;135(3):732-741

COSMETIC

The Efficacy and Safety of Liquid-Type Botulinum Toxin Type A for the Management of Moderate to Severe Glabellar Frown Lines

Jung Eun Kim, M.D.
Eun Jong Song, M.D.
Gwang Seong Choi, M.D.
Bark-Lynn Lew, M.D.
Woo-Young Sim, M.D.
Hoon Kang, M.D.

Seoul and Incheon, Republic of Korea

Background: Botulinum toxin type A has been widely used to correct unwanted hyperfunctional facial lines. Most forms of botulinum toxin type A currently used require reconstitution, which is very inconvenient for users. The authors compared the efficacy and safety of a newly developed liquid-type botulinum toxin type A (MT10109L) and onabotulinumtoxinA (Botox) for moderate to severe glabellar lines.

Methods: A double-blind, randomized, active drug–controlled, phase III study with 168 enrolled subjects was performed. The primary efficacy endpoint was the improvement rate at maximum frown at week 4 by the investigators' live assessment. The secondary efficacy endpoint included the improvement rate at maximum frown at week 16 and at rest at weeks 4 and 16 by live assessment, and the improvement rate at maximum frown and at rest based on photographic assessment at week 4. Self-assessment and self-satisfaction with glabellar line improvement were also evaluated.

Results: The improvement rate at maximum frown by live assessment was not significantly different between the MT10109L and Botox groups. In addition, the improvement rate of glabellar lines at rest based on the investigators' live assessment and photographic assessment was similar in both treatment groups. However, the improvement rate at maximum frown by live assessment at week 16 was significantly higher in the MT10109L group compared with the Botox group. There were no severe adverse events.

Conclusions: The efficacy and safety of MT10109L were comparable to those of Botox for the management of glabellar frown lines. MT10109L provides greater convenience because it does not require dilution and has long-lasting effects. (*Plast. Reconstr. Surg.* 135: 732, 2015.)

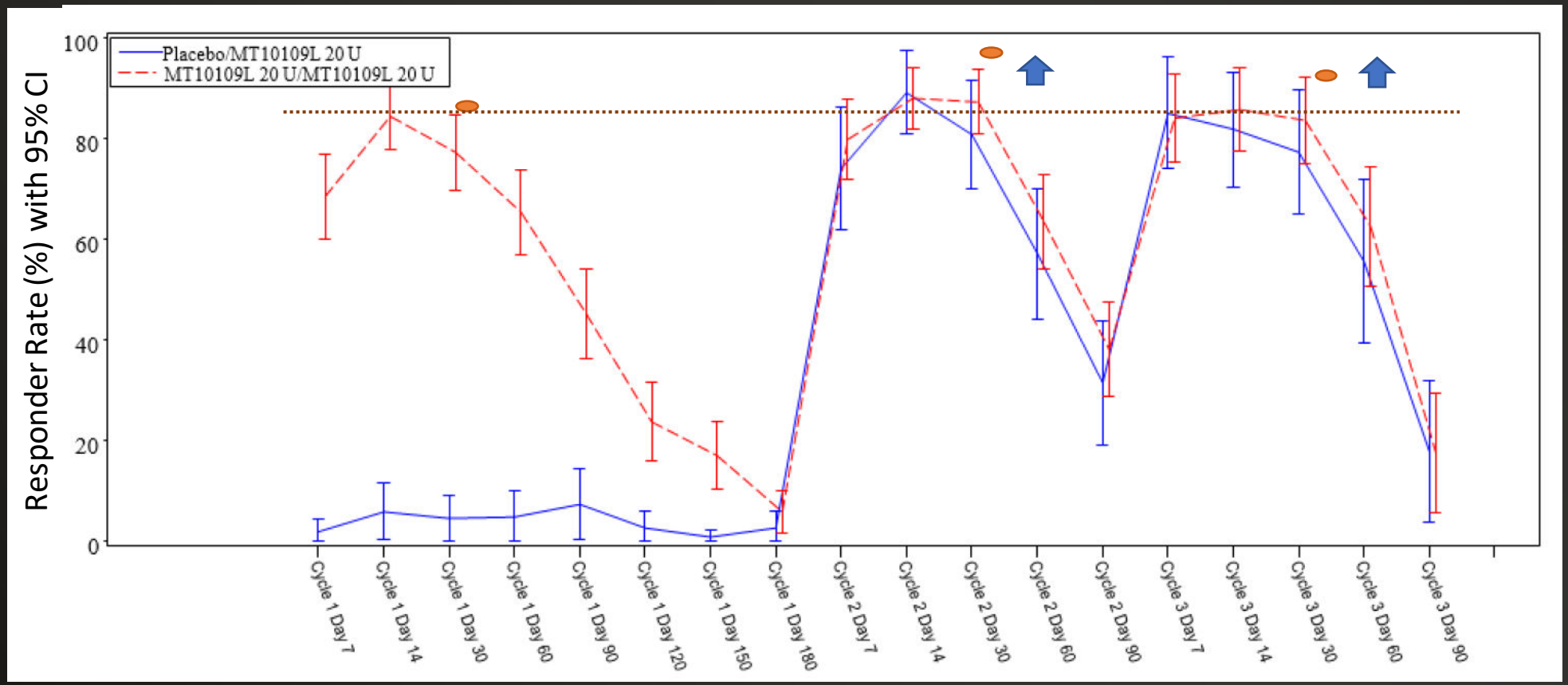
CLINICAL QUESTION/ LEVEL OF EVIDENCE: Therapeutic, II.

NivobotulinumtoxinA (MT10109L)

Introduction

INVESTIGATOR RATED REDUCTION OF GL SEVERITY

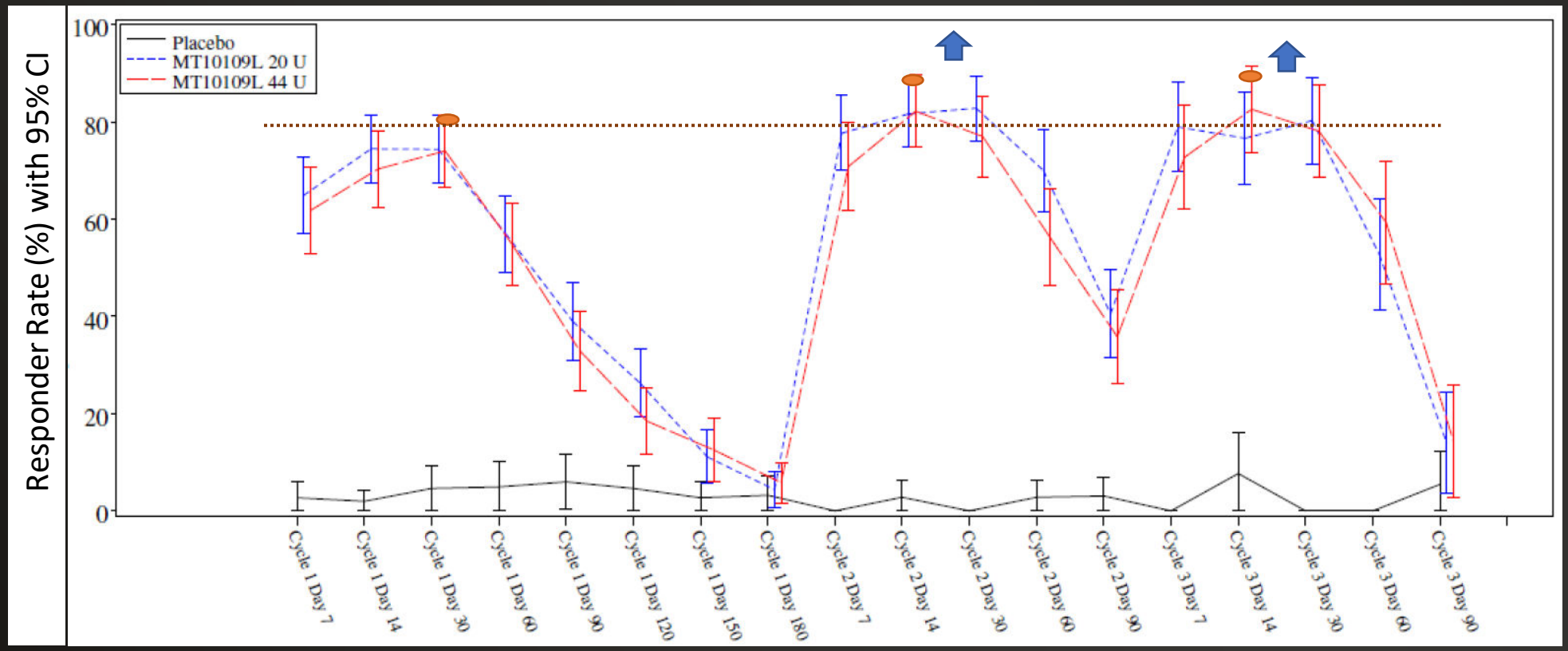
Study 001: Proportion of Participants Achieving an Investigator FWS Rating of None or Mild Injection Cycles 1, 2 and 3. Glabellar lines only.



NOTE: mITT population - all randomized participants who had a baseline transformed FLO-11 questionnaire total score of ≤50

INVESTIGATOR RATED REDUCTION OF GL SEVERITY

Study 005: Proportion of Participants Achieving an Investigator Rating of <u>None or Mild</u>
Cycles 1, 2, 3. Glabellar lines with or without Lateral Canthal Lines.

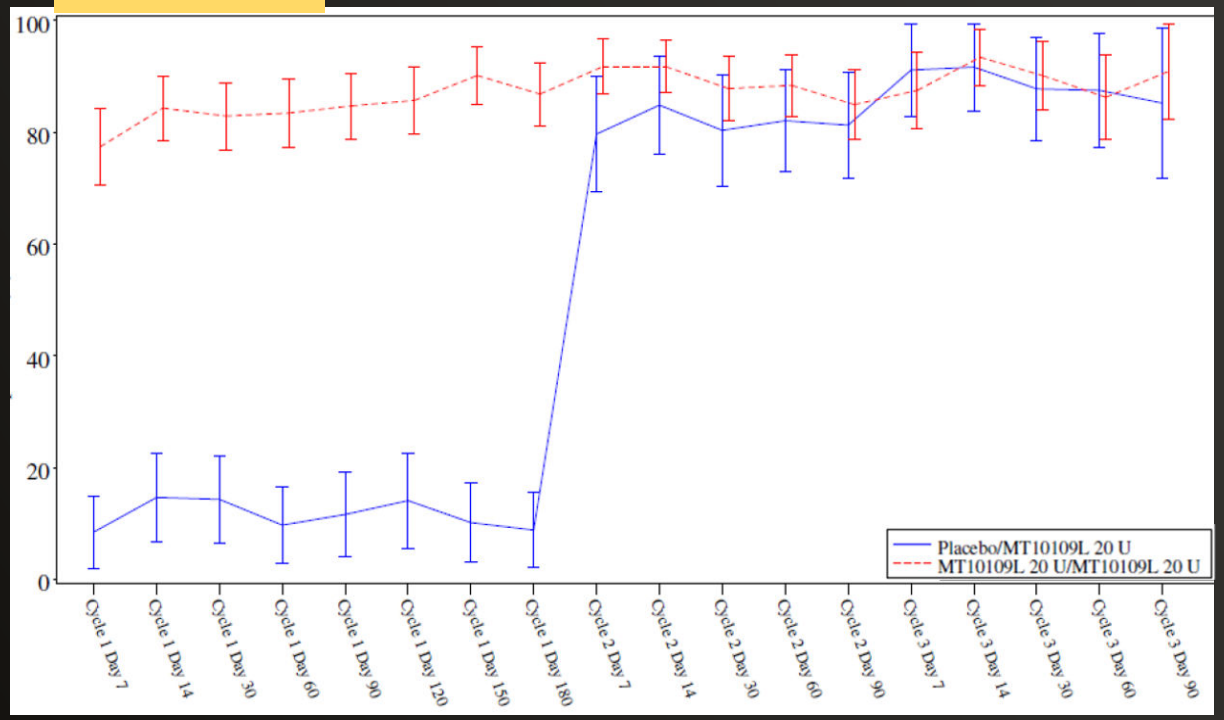


mITT population - all randomized participants who had a baseline transformed FLO-11 questionnaire total score of ≤50

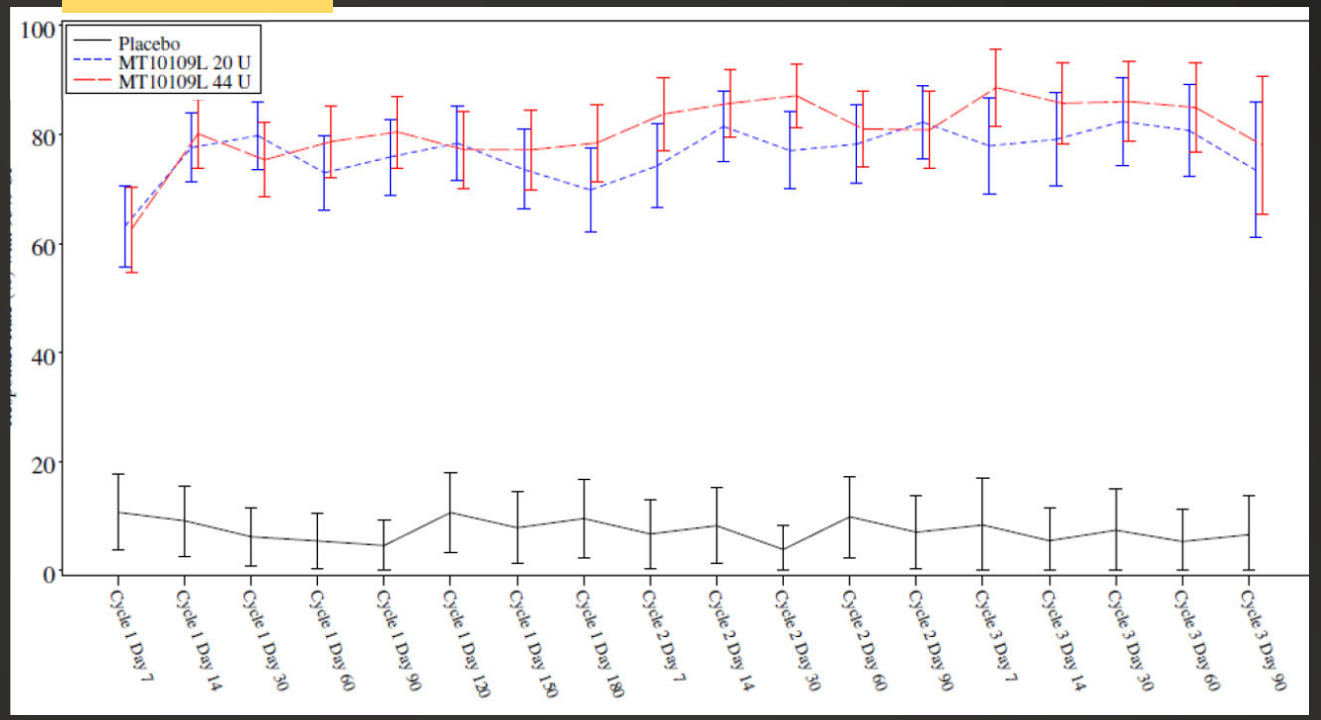
GL SUBJECT SATISFACTION (FLSQ)

Proportion of Participants Reporting Mostly Satisfied/Very Satisfied*

STUDY 001



STUDY 005



* on the FLSQ Follow-up Version Item 5 (ITT population)

TREATMENT EMERGENT ADVERSE EVENTS

Study Drug-Related Treatment-Emergent Adverse Events

Occurring in **≥5%** of Participants in Any Treatment Group (Safety Population)

	Study 001		Study 005		
	Placebo (N=80)	20U (N=223)	Placebo (N=82)	20U (N=174)	44U (N=159)
Participant with at least one TEAE – N (%)	35 (43.8)	118 (52.9)	31 (37.8)	82 (47.1)	61 (38.4)
Headache – N (%)	4 (5.0)	22 (9.9)	4 (4.9)	14 (8.0)	6 (3.8)
Injection site pain – N (%)	4 (5.0)	16 (7.2)	4 (4.9)	9 (5.2)	7 (4.4)

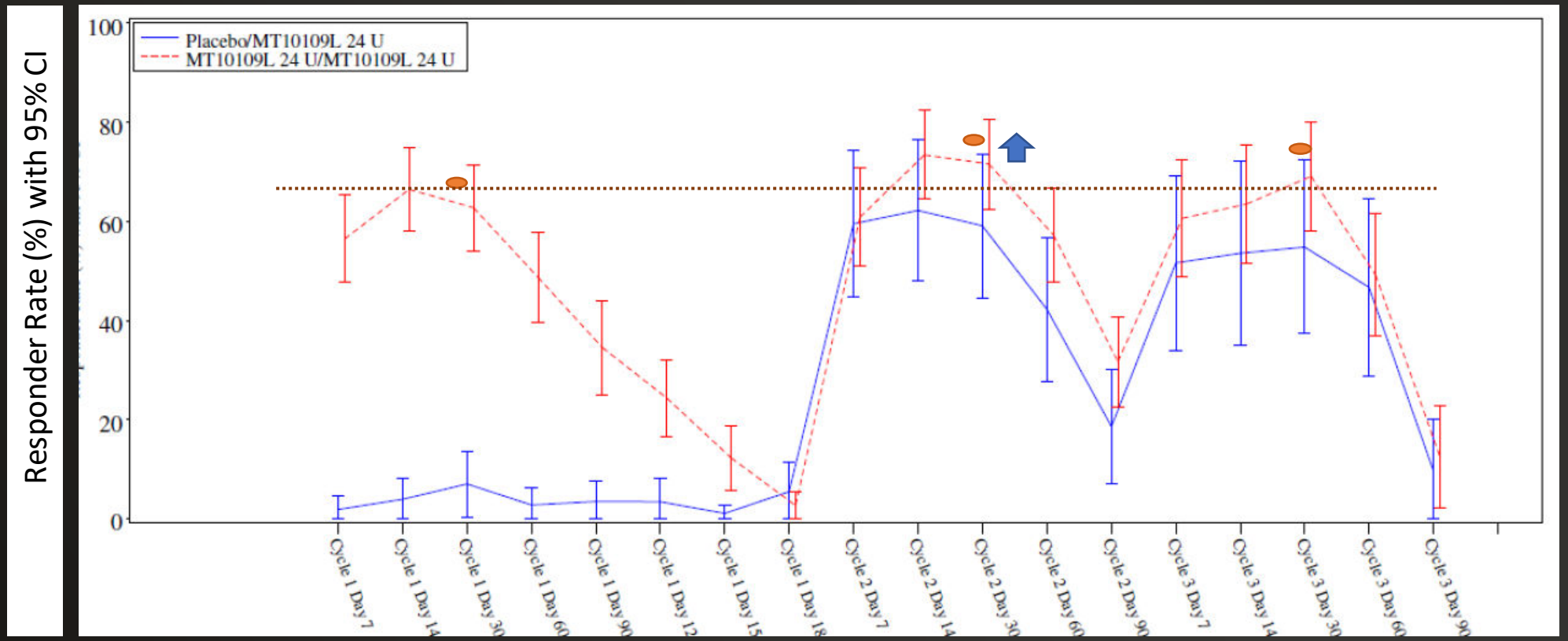
CONCLUSION – GLABELLAR CLINICAL RESEARCH

Treatment of glabellar lines MT10109L 20U over 3 treatment cycles was efficacious, safe and well tolerated in both male and female participants (with or without concurrent lateral canthal lines)

- statistically significant improvements were observed with MT10109L compared to placebo
- MT10109L was safe and well tolerated

INVESTIGATOR RATED REDUCTION OF LCL SEVERITY

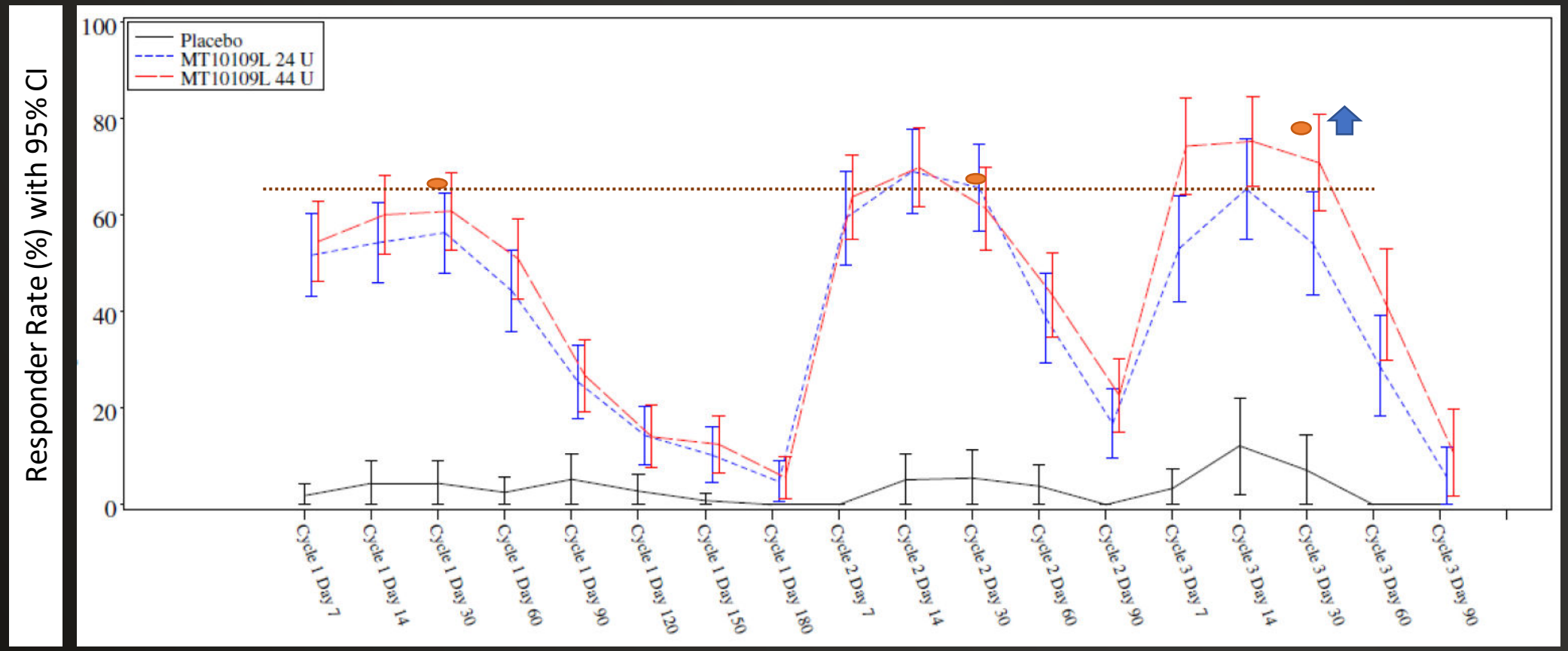
Study 002: Proportion of Participants Achieving Investigator Rating of None or Mild
Cycles 1, 2, 3. Lateral Canthal Lines only



mITT population - all randomized participants who had a baseline transformed FLO-11 questionnaire total score of ≤50

INVESTIGATOR RATED REDUCTION OF LCL SEVERITY

Study 006: Proportion of Participants Achieving Investigator Rating of None or Mild
Cycles 1, 2, 3. Lateral Canthal Lines with or without Glabellar lines.

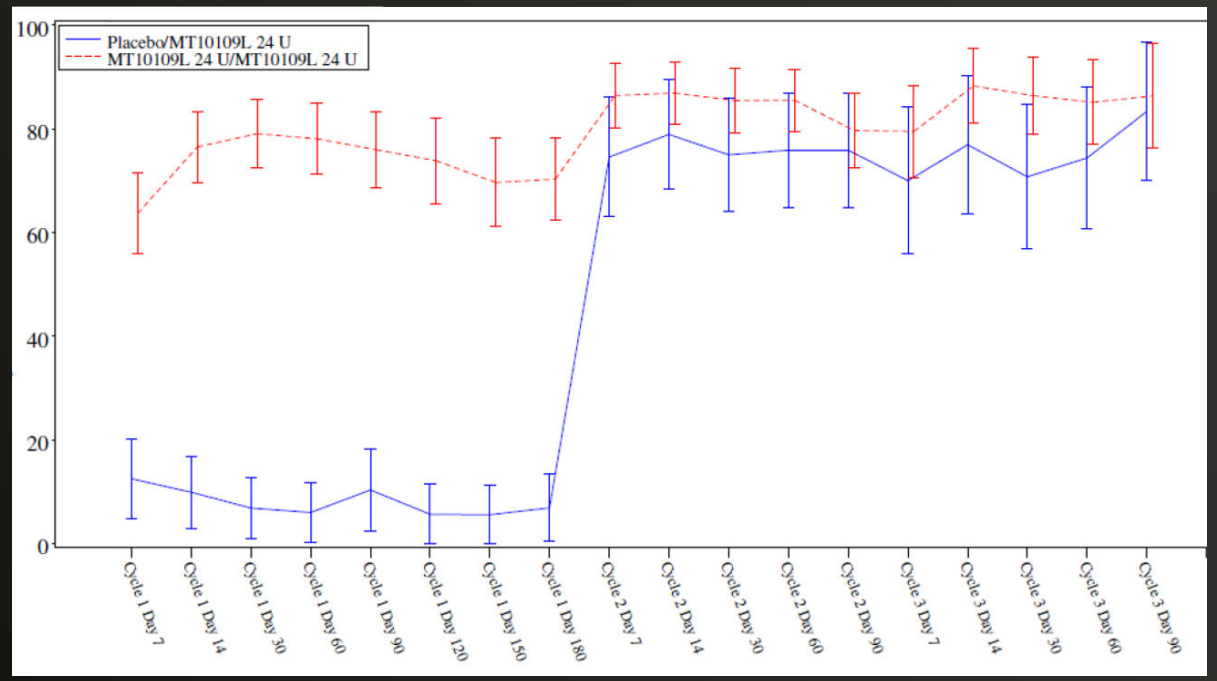


mITT population - all randomized participants who had a baseline transformed FLO-11 questionnaire total score of ≤50

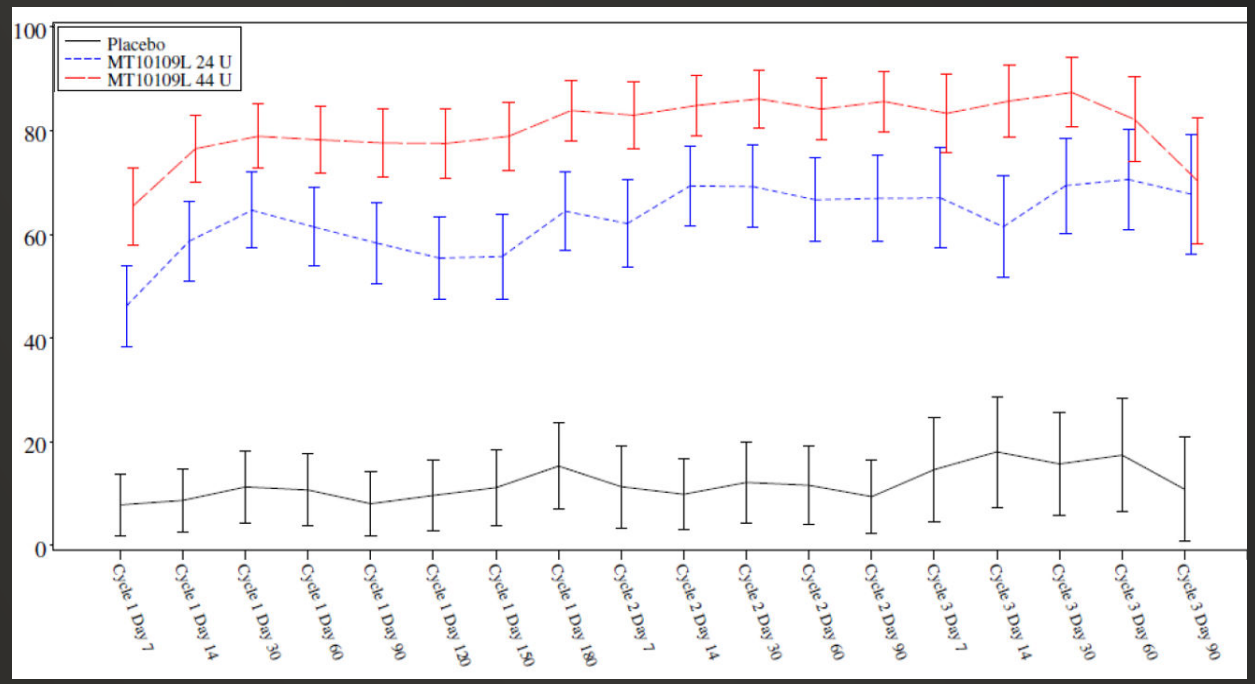
LCL SUBJECT SATISFACTION (FLSQ)

Proportion of Participants Reporting Mostly Satisfied/Very Satisfied

STUDY 002



STUDY 006



* on the FLSQ Follow-up Version Item 5 (ITT population)

TREATMENT EMERGENT ADVERSE EVENTS

Study Drug-Related Treatment-Emergent Adverse Events

Occurring in **≥5%** of Participants in Any Treatment Group (Safety Population)

	Study 002*		Study 006		
	Placebo (N=76)	24 U (N=223)	Placebo (N=86)	24 U (N=171)	44 U (N=168)
Participant with at least one TEAE – N (%)	12 (15.8)	78 (35.0)	50 (58.1)	90 (52.6)	106 (63.1)
Headache – N (%)	-	5 (2.2)	3 (3.5)	9 (5.3)	22 (13.1)
Nasopharyngitis – N (%)	1 (1.3)	3 (1.3)	6 (7.0)	16 (9.4)	15 (8.9)
Upper respiratory tract infection – N (%)	-	2 (0.9)	5 (5.8)	4 (2.3)	10 (6.0)
Injection site pain – N (%)	-	1 (0.4)	8 (9.3)	15 (8.8)	15 (8.9)
Injection site hemorrhage – N (%)	1 (1.3)	7 (3.1)	6 (7.0)	9 (5.3)	6 (3.6)
Injection site bruising – N (%)	-	2 (0.9)	6 (7.0)	7 (4.1)	6 (3.6)

* Study 002: No TEAEs occurred in ≥5% for any treatment group

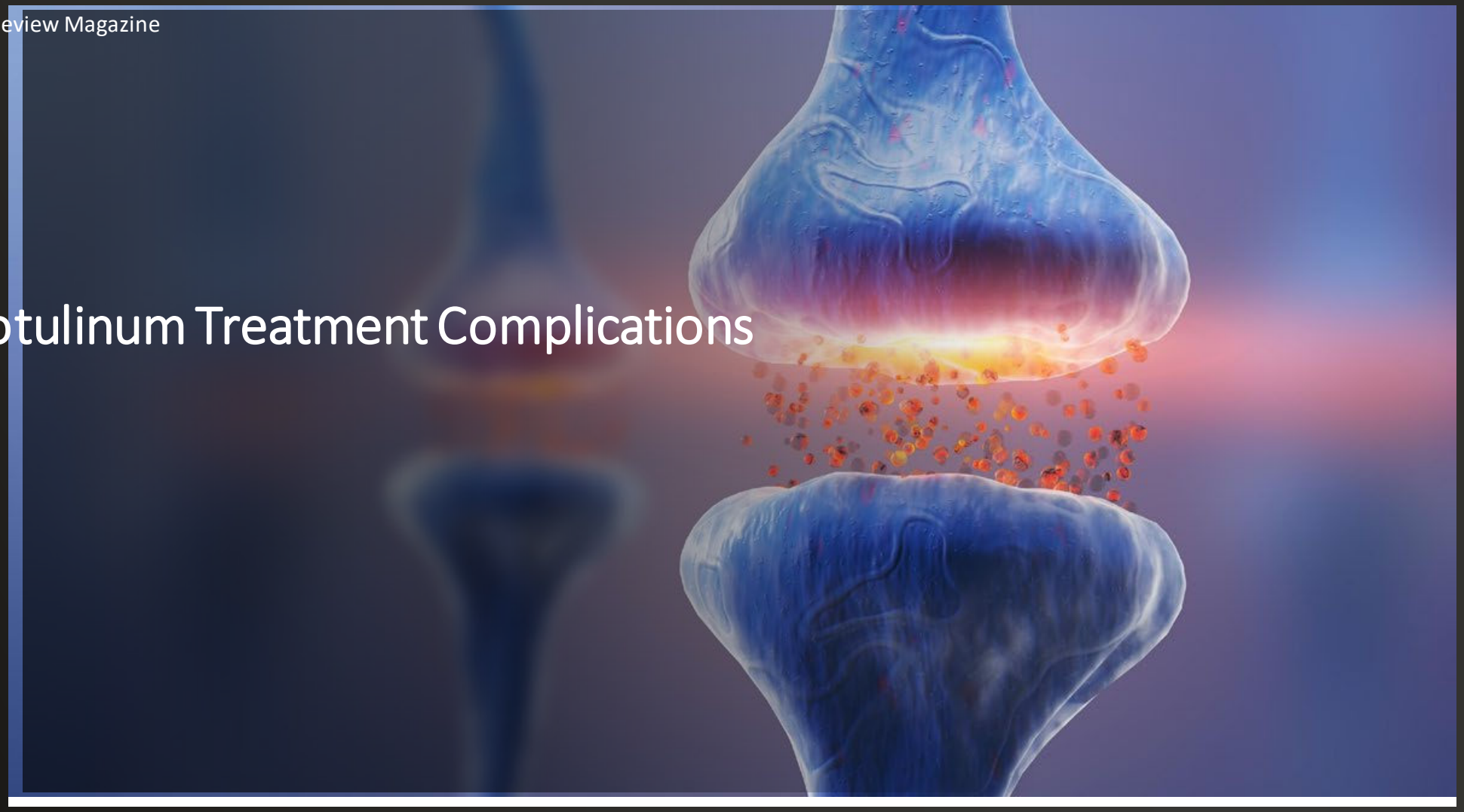
CONCLUSION – LATERAL CANTHAL LINES CLINICAL RESEARCH

Treatment of lateral canthal lines with 24 units of MT10109L over 3 treatment cycles was efficacious, safe and well tolerated in both male and female participants (with or without concurrent glabellar lines)

- statistically significant improvements were observed with MT10109L compared to placebo
- MT10109L was safe and well tolerated

ReViVox - DelNova Medical

- Editor’s Choice
- Top 10 Biotech Startups
- 2022 Life Sciences Review Magazine



Solving Botulinum Treatment Complications

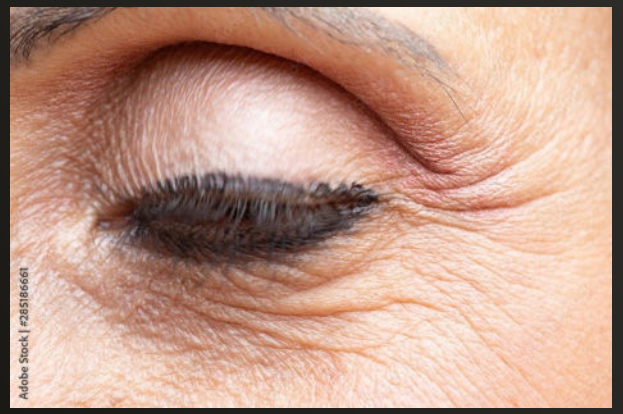
Reversing BoNT Toxin Treatment

Problem

BoNT ADVERSE EVENTS

Most common are transient side-effects, persisting from weeks to months

Yet, there is no approved or effective treatment



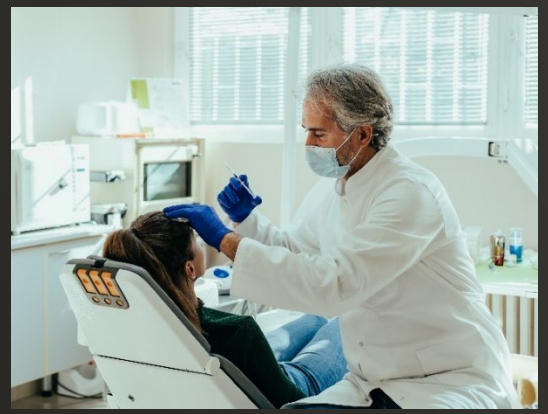
Solution

DELNOVA'S REVIVOX®

Solves adverse events by reversing undesirable paralysis

Limits reversal to problem areas maintaining intended therapy

intact

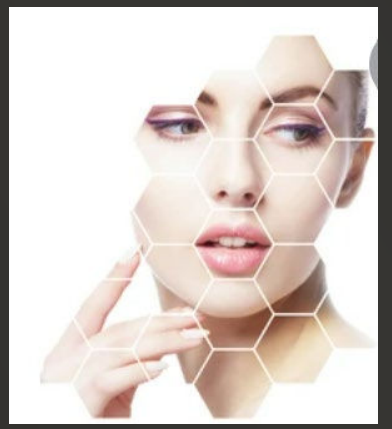


Impact

BENEFITS

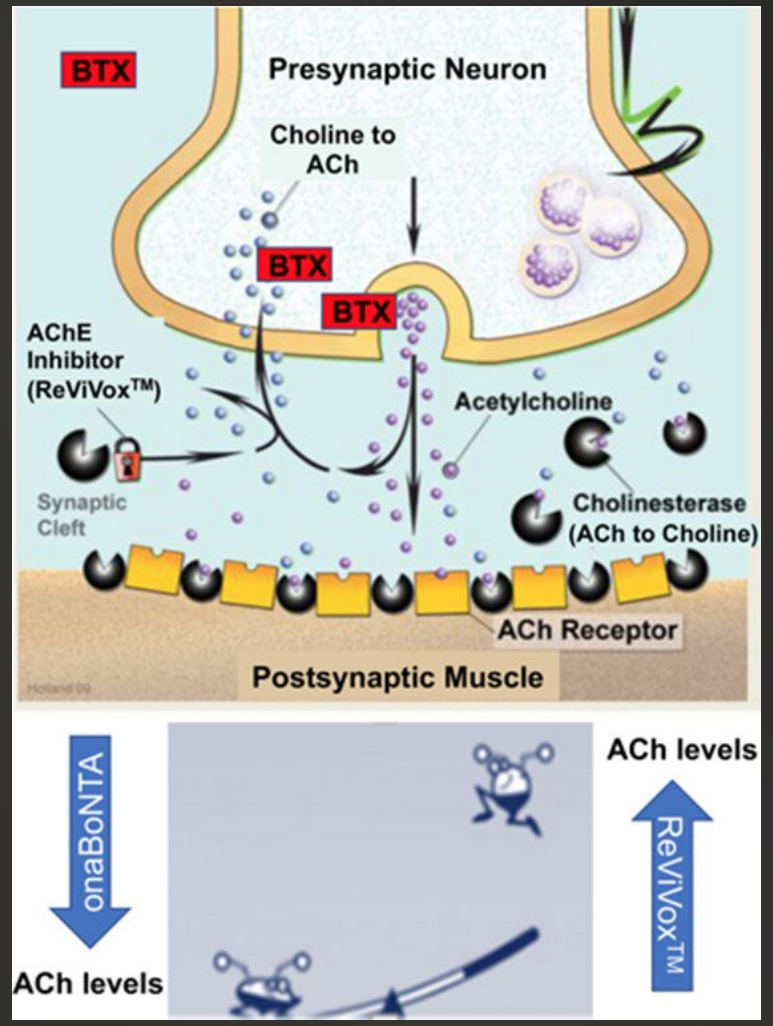
Improves Outcomes and patient safety

Reduces hesitancy & increases sales of BoNT treatments



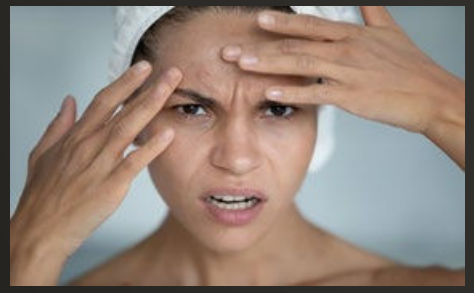
Mechanism of Action – Anticholinesterase AChE to counteract the Inhibitor

- BoNT blocks the release of the neurotransmitter acetylcholine
- Outside the neuron, endogenous enzyme (inhibitor) cholinesterase normally breaks down and decreases levels of acetylcholine
- counteracts by attacking the enzyme acetylcholinesterase (inhibitor) and thereby increases acetylcholine (neurotransmitter)
- Opposing effect serves to re-establish neurotransmission



Innovation for Aesthetics

Why?



Potential Side Effect from Neurotoxins – [eg Botox®]

Every pencil needs an eraser

With HA(Hyaluronic Acid) Fillers we have an eraser

NOW for toxins

*** Under Development**

Spotlight On: ReViVox

A look at the first emerging solution to reverse the effects of botulinum toxin

While botulinum toxin is considered the most popular non-surgical aesthetic procedure, it has been estimated that one in six patients suffer from some kind of complication following the treatment.[1] Some of the common include ptosis and facial paresis,[1] as well as an unsatisfactory aesthetic result.

While hyaluronic acid dermal fillers have hyaluronidase, toxin has been left without an "eraser" and there are currently limited methods to successfully combat these adverse effects. However, a promising new formulation might be about to change this.

Formulation of ReViVox

In 2016, biochemical engineer Mary Gardner was approached by a woman suffering from ptosis after botulinum toxin treatment. This side effect has been noted in the literature, with pharmaceutical company Allergan Aesthetics revealing in a multicentre post-marketing US Food and Drug Administration study that there was a 4.6% incidence of ptosis (12 out of 263) after injection.[2]

Despite this, Gardner could find no solution to the complication. This unmet need led her to start investigating the gap in the market and begin formulating the first injectable to reverse toxin side effects, ReViVox. The product is based on the active pharmaceutical ingredient, an anticholinesterase, small molecule drug that is already used to treat other medical conditions such as reversal of neuromuscular blockade in anesthesia or myasthenia gravis.[3] Gardner explains, "Botulinum neurotoxin functions by inhibiting the release of the neurotransmitter acetylcholine. Normally, outside the neuron, the endogenous enzyme cholinesterase acts as an inhibitor, breaking down and reducing acetylcholine levels. ReViVox intervenes by targeting the enzyme acetylcholinesterase (inhibitor), thereby augmenting acetylcholine concentrations. This opposing effect is instrumental in restoring neurotransmission, thus serving to re-establish the proper functioning of neuronal communication pathways."

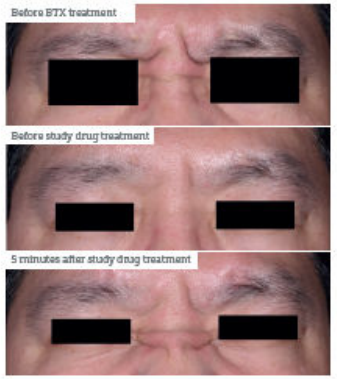


Figure 1: Maximum contraction of the glabella (A) before BTX treatment, (B) before study drug treatment, and (C) five minutes after study drug treatment.[5]

Animal and human studies

In initial proof-of-concept animal trials, rats injected with botulinum toxin into the masseter muscles experienced frozen jaw muscles, resulting in diminished food intake and weight loss. Among the animals treated with the anticholinesterase to reverse this effect, a complete restoration of food intake was observed by day 26 of the study. In contrast, the control animals had still not recovered by day 37.[4]

In humans, a recent study conducted by chief medical strategist Dr Steve Yoelin investigated the effect of the active ingredient in ReViVox in six patients over the age of 18 with moderate to severe glabellar lines. The individuals received Botox (BTX) treatment initially, followed by randomised administration of either saline (placebo; n=3) or the study drug (n=3) approximately two weeks later. Subjects initially assigned to the placebo group subsequently underwent crossover to receive the study drug as well. Canfield photography of the glabella was conducted at intervals of five, 15, 30, 60, 120, and 180-minutes post-intervention or until the subject returned to baseline within one hour. Blinded evaluation of the Canfield photographs was performed using a four-point Facial Wrinkle Scale (FWS).[5]

Among those treated with ReViVox, subjects exhibited increased wrinkle severity during maximum frown, demonstrating a 60% responder rate compared to the placebo group. Notably, all responders returned to baseline wrinkle severity post-dose. A representative image of a responding subject is depicted in **Figure 1**.[5]

Several subjects displayed restored muscle movement in the glabellar region, as assessed by a four-point FWS evaluation. The findings suggest that ReViVox holds promise as a potential rescue agent for mitigating undesirable localised outcomes associated with neurotoxin treatment, as this is the first human demonstration of the reversal of muscle weakness caused by a neurotoxin via a local muscle injection.[5] Founder of the cosmetic uses of botulinum toxin, Dr Jean Carruthers, is currently involved in the research and trials of ReViVox. On her involvement, she commented, "ReViVox addresses a huge unmet need. For many years, clinicians and patients have wished for an injectable local and focal 'eraser' for unwanted neuromodulator side effects such as eyelid or brow ptosis. Previous 'eraser' medications have been given systemically. It makes sense to solve a local problem locally!"

The future of ReViVox

Currently, both human and animal studies have indicated the efficacy of the product, but final completion is estimated to happen in two to three years' time. During this period, a Phase 1/2 clinical study with 125-160 subjects and a Phase 3 pivotal study will be conducted, before the product will be approved and available for wider use.

A final formulation of ReViVox is projected to be longer lasting.

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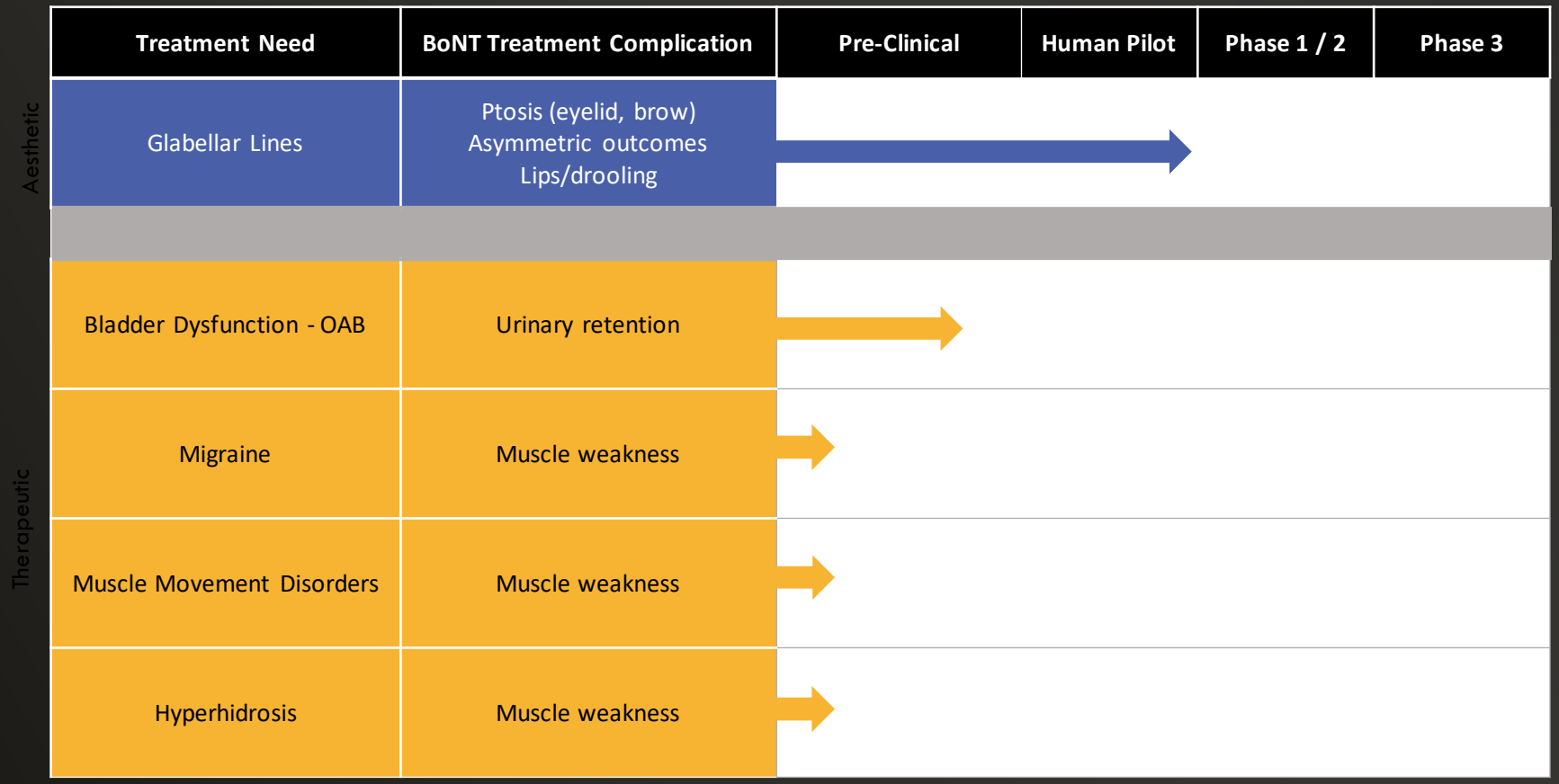
1. D Zargaran et al., Complications of facial cosmetic botulinum toxin A injection: Analysis of the UK Medicines & Healthcare Products Regulatory Agency registry and literature review, Journal of Plastic Reconstructive & Aesthetic Surgery, 2021
2. Clin M. "Management of Ptosis" J Clin Aesthet Dermatol. 2016 Dec
3. NHS, Pyridostigmine drug information, <https://www.cuh.nhs.uk/patient-information/pyridostigmine-drug-information/>
4. DelNova, data on file, 2021
5. Yoelin Et al., Demonstration of the potential for ReViVox in Reversing the Local Effect of Toxin, 2023, <https://delnova.net/2023/08/08/delnova-announces-first-in-human-demonstration-of-reversal-of-neurotoxin-muscle-weakness/>

ReViVox Development Pipeline



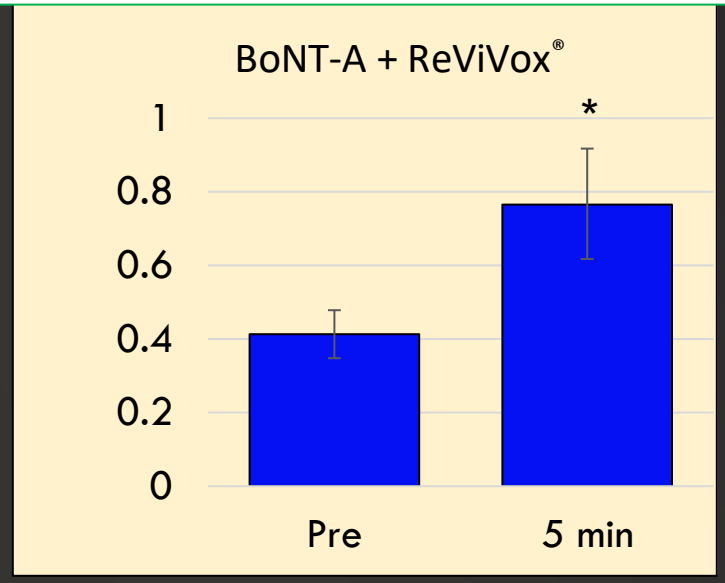
Clinical Strategy and Rationale

- Addresses adverse effects after they are realized (contrary to an antitoxin)
- Targets afflicted muscle by local injection
  - primary treatment intact
  - reduced systemic effects
- API is a small molecule, readily available, off-patent, and has decades of safety data in humans
- Low manufacturing cost relative to biologics
- Attractive product margin anticipated for ReViVox®

Summary of Prior Pre-Clinical Findings

- Multiple lines of evidence show rapid functional recovery after ReViVox treatment in BoNT-paralyzed muscles
  - Rat feeding model (masseter paralysis)
  - High-resolution contractile testing
    - Rat masseter paralysis and rescue
    - Rat hindlimb (tibialis anterior) paralysis and rescue
    - Rat bladder paralysis and rescue
- BoNT- and ReViVox-dose dependent effects
- Stimulation frequency dependent effects

Contractile Function Enhanced by ~90% with ReViVox®



Medium dose of ReViVox®, @30Hz

* p<0.02 (effect of ReViVox®; paired t-test)

DelNova's Drug Development Approach

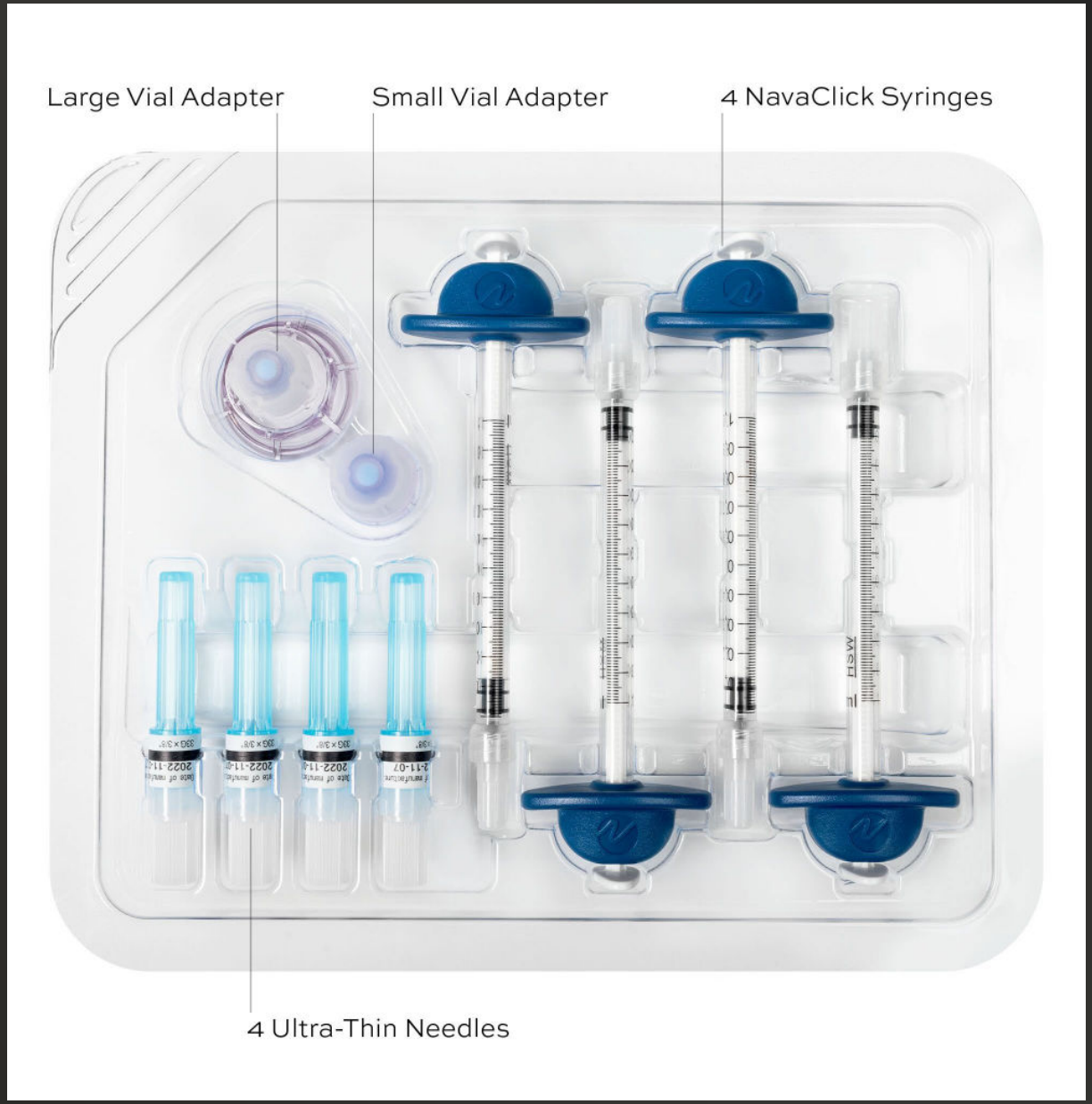
- A novel formulation will result in a use-specific target product profile with a different route of administration and repurposed API for a novel indication
- The US FDA regulatory approval is expected to be a 505b2 abbreviated pathway which takes advantage of previously documented scientific and clinical data of the API
- Pursuing the aesthetic indication first offers the shortest and least expensive path to FDA approval and commercialization
- A rare disease (Orphan Drug Status) could be pursued for Therapeutic indication such as Cervical Dystonia

NavaClick by Lineage Medical

A Complete Solution

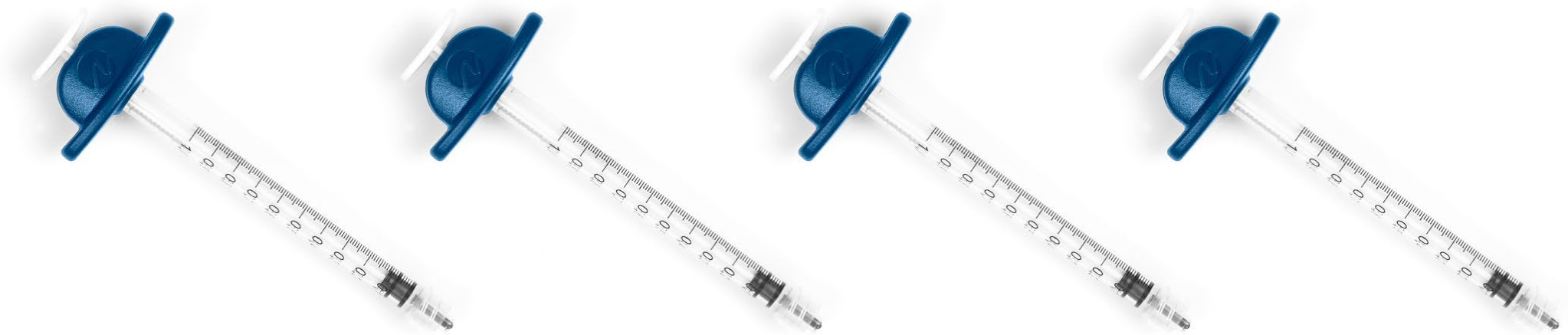
The System modernizes th e entire procedure – from reconstitution to injection – with significant benefits to

- The Practice
- The Practitioner
- The Patient.



In the Kit: Four NavaClick Syringes

The Centerpiece of the System



The Syringe

THREE KEY ADVANTAGES

1. Audible and Tactile Feedback
2. Precision Dosing
3. Reduced Neurotoxin Waste

Audible and Tactile Feedback

"The desired volume of fluid can be incrementally delivered accurately and precisely without visually monitoring the position of the plunger."[1]

Practitioners no longer measure dosage based on visual tracking of the graduation marks. They use a multi-sensory approach that allows them to keep t heir eyes on the patient.

The result is "liberating."[2]

Each Feedback Click = 0.02 mL

- Molded detents in the plunger provide accurate and precise incremental dosing

Precision Dosing

ACCURACY

- The NavaClick is approximately **4 - 10x more accurate** than the ISO 7886-1 requirements for accuracy of printed graduation lines.

	Ideal Expelled Volume	ISO 7886-1 Printed Graduation Accuracy Requirement	NavaClick Max. Deviation from Ideal (n=29)
10 Clicks	0.2 mL	± 0.019 mL (± 9.5%)	± 0.005 mL (± 2.5%)
20 Clicks	0.4 mL	± 0.023 mL (± 5.75%)	± 0.008 mL (± 2%)
30 Clicks	0.6 mL	± 0.030 mL (± 5%)	± 0.007 mL (± 1.2%)
40 Clicks	0.8 mL	± 0.040 mL (± 5%)	± 0.009 mL (± 1.1%)
50 Clicks	1.0 mL	± 0.050 mL (± 5%)	± 0.005 mL (± 1%)

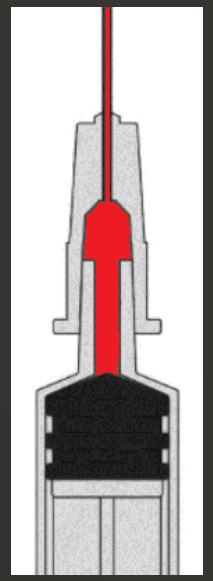
RELIABILITY

- The NavaClick consistently and predictably delivers the same amount of fluid each time within a standard deviation of .0044 mL.

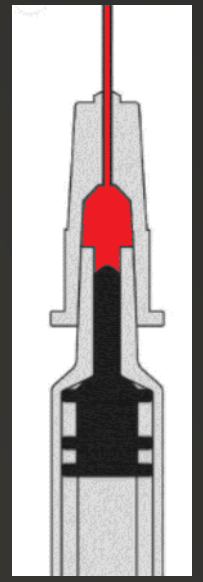
	NavaClick Standard Deviation (95% CI) (n=29)
10 Clicks	± 0.0044 mL

Reduced Neurotoxin Waste

Standard Syringe
Standard Needle



LDS Syringe
Standard Needle



NavaClick
LDS Syringe
LDS Needle

- Low dead space (LDS) syringe and needle design.

  Save up to 0.04 mL (avg. 0.025 mL) per syringe when compared to using an LDS luer syringe with a standard luer needle hub.

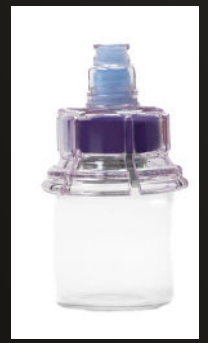
- Eliminate waste due to over-injecting.

  NavaClick dispenses precisely the amount desired at each insertion point.

Image Sourced: DOI:10.1186/s12954-017-0207-5

In the Kit: Two Vial Adapters

LARGE
20mm

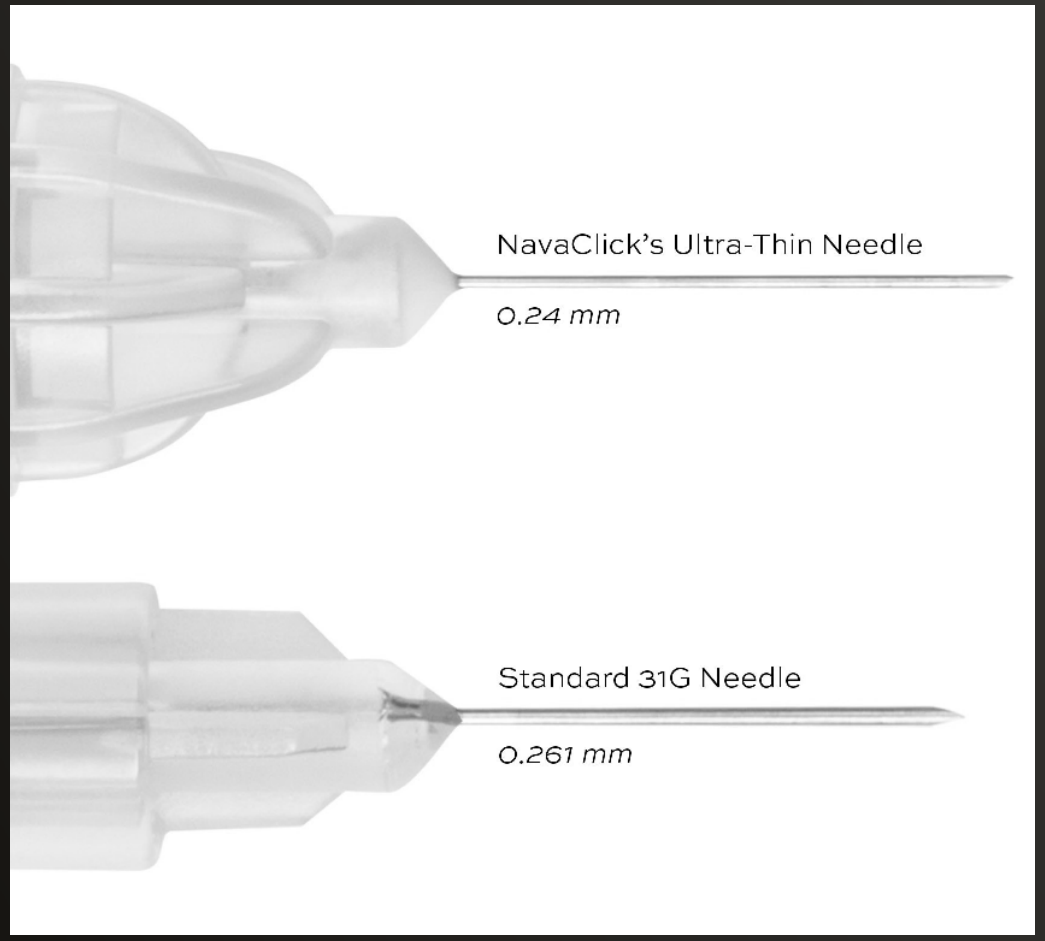


SMALL
13mm

In addition to making preparation easier and more efficient, the sterile vial adapters provide:

- Aseptic, no-spill access to the any neurotoxin.
- Needle-free reconstitution and withdrawals t hrough a swabable, luer-lock top.

In the Kit: Four Hypodermic Needles



Practitioners and patients appreciate the quality of the needles that come bundled in the kit. The needles are:

- Low Dead Space.
- Ultra-fine, measuring 0.24mm x 9mm.
- Ultra-sharp – and they stay sharp.