HAUTÄRZTE
RZANY & HUND

IncobotulinumtoxinA for Upper Facial Lines

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Nottingham

Berthold Rzany

Before we start …..

- *Evidence wise* we are with all botulinum toxins on the good side as all toxins are drugs and drugs require clinical controlled trials

but let‘s have a general look on botulinum toxin first!

At the moment we have three different toxins in Europe and the US

- *Abo* - BoNT-A (Dysport /Azzalure)
- *Inco* - BoNT-A (Xeomin /Bocouture)
- *Ona* - BoNT-A (Botox /Vistabel)

They are different,
but they behave all similar when injected

Studies on the dissociation of botulinum neurotoxin type A complexes

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ABSTRACT

The neurotoxins produced by the various strains of the anaerobic bacterium *Clostridium botulinum* naturally occur associated with complexing proteins which serve to protect the neurotoxins from the harsh environment of the mammalian gastrointestinal tract during bacterial invasion of the host. Three different complex species with the discrete sizes 19S (900 kDa, LL complex), 16S (500 kDa, L complex) and 12S (300 kDa, M complex) may be isolated from *C. botulinum* type A cultures. However, to affect their target cells these complexes must dissociate releasing the free 150 kDa neurotoxin.

This study assesses the stability of these *Clostridium botulinum* neurotoxin serotype A (BoNT/A) complexes and identifies factors which influence their dissociation. The knowledge gained with purified toxin complexes was subsequently employed to analyze the presence of such complexes in the freeze or spray-dried commercial BoNT/A products Botox and Dysport in comparison to the complexing protein free product Xeomin.

Purified 900 kDa and 500 kDa toxin complex preparations show a pH and time dependent release of the 150 kDa neurotoxin with a half-life of less than a minute at pH values >7.0. At pH values of 6.25 or less, the complexes are stable. Furthermore, dilution of concentrated 900 kDa complexes leads to dissociation into 500 kDa, neurotoxin containing complexes. Addition of sodium chloride as contained in isotonic saline leads to further disruption of these complexes resulting in the release of the free 150 kDa neurotoxin.

Examination of the commercial botulinum neurotoxin products Botox and Dysport using the same analytical procedures leads to the same conclusion: the dilution, drying and reconstitution processes of these products lead to a complete dissociation of 900 kDa complexes and 85% or more of neurotoxin are present in free form.

Conclusion: BoNT A toxin complexes have evolved to quickly respond to specific environmental changes by efficient release of the neurotoxin. During pharmaceutical production and reconstitution of BoNT A products, the same principles effect the quantitative dissociation of 900 kDa complexes and release of free neurotoxin prior to injection into target tissues.

And all three preparations have the same 150 kd component

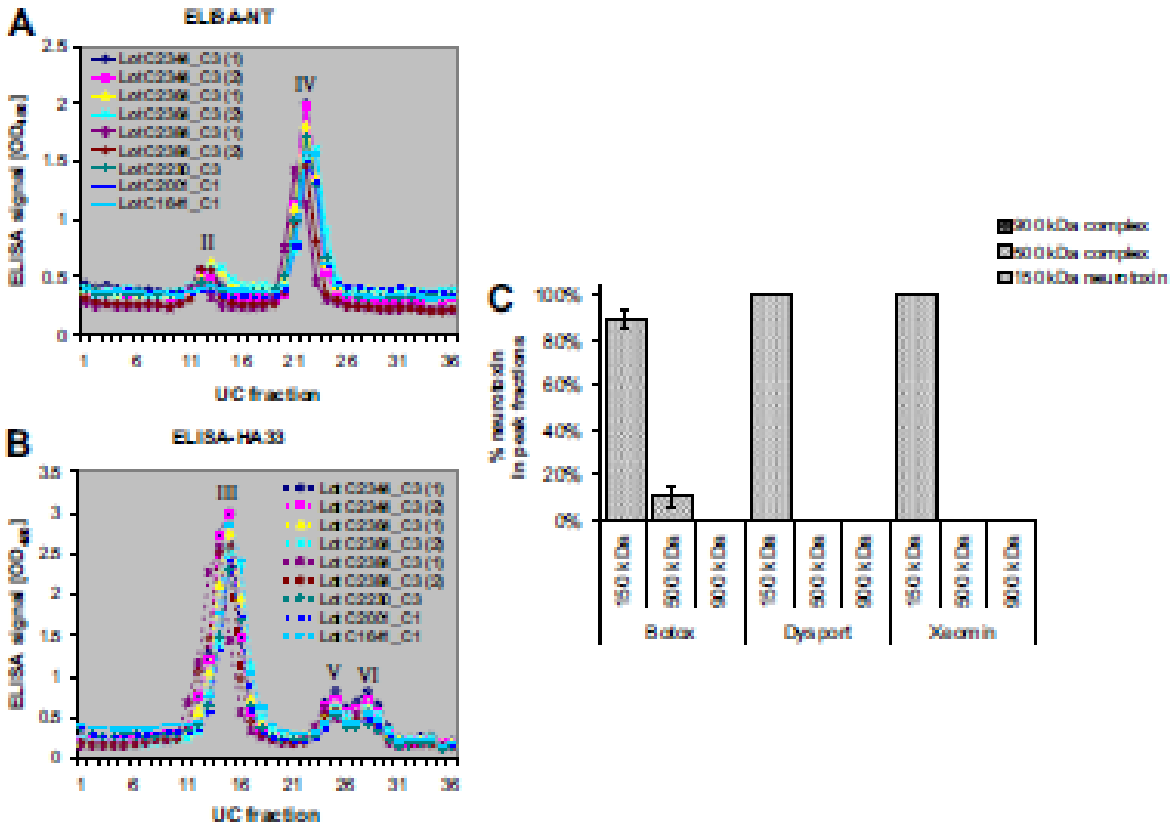
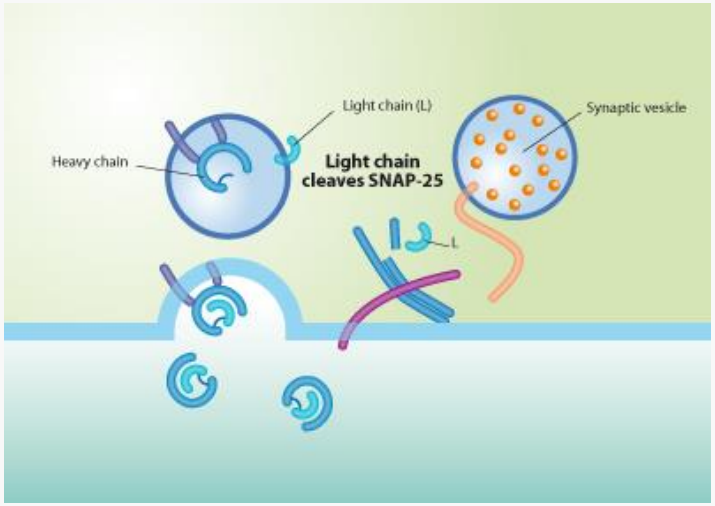


Fig. 7. Analysis of BoNT/A complex size of commercially available Botox lots ($n = 9$) by sedimentation velocity analysis. Peaks are labeled as follows: II: neurotoxin containing 16S (~500 kDa) complex, III: neurotoxin-free complex, IV: free, 150 kDa neurotoxin. Sedimentation profile of non-formulated BoNT/A complex after dilution with either 0.9% NaCl/0.5% HSA or with 0.94% sucrose/0.2% HSA; fraction analysis by ELISA-NT.

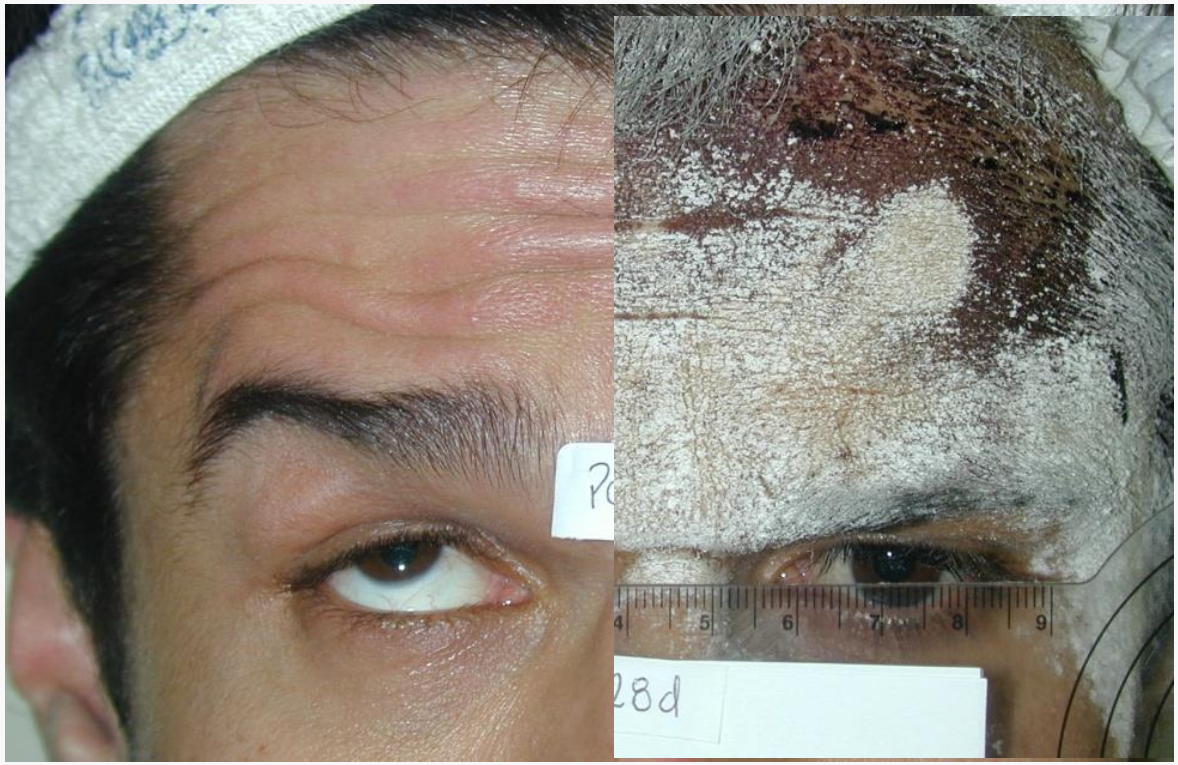
They decrease muscular activity*

- Botulinum toxin *specifically prevents neurosecretory vesicles from docking/fusing with the nerve synapse plasma membrane* and releasing their neurotransmitters to the adjacent muscle fibers.



* as well as sweating

Decrease of muscular activity and sweating around 2 injection points



The area of the field of effect is influenced by the

- Units injected
- Muscles size and activity*

* Respectively the activity of the sweat glands

They are studied and licensed for ONE aesthetic indication mostly

- The glabella

Here one study with another botulinum toxin as comparator

Noninferiority of IncobotulinumtoxinA, Free from Complexing Proteins, Compared with Another Botulinum Toxin Type A in the Treatment of Glabellar Frown Lines

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BACKGROUND Use of botulinum toxin for esthetic purposes has rapidly expanded over the last 20 years. IncobotulinumtoxinA, also known as NT 201, is a new botulinum toxin type A (150 kDa) that is free from complexing proteins.

OBJECTIVES A prospective, multicenter, randomized, rater- and patient-blind, international Phase III trial to investigate the noninferiority of incobotulinumtoxinA to another botulinum toxin type A, onabotulinumtoxinA, in the treatment of glabellar frown lines.

METHODS A total of 381 patients were randomized in a 3:1 (incobotulinumtoxinA:onabotulinumtoxinA) ratio to receive 24 U incobotulinumtoxinA of or onabotulinumtoxinA. Efficacy end points included the percentage of responders (patients with an improvement of $\geq$ 1 point on a 4-point facial wrinkle scale) at maximum frown at weeks 4 and 12 as assessed by the investigators, and a panel of independent raters based on standardized digital photographs.

RESULTS Four weeks after injection, response rates at maximum frown were 96.4% in the incobotulinumtoxinA group and 95.7% in the onabotulinumtoxinA group as assessed by independent raters. Analysis of the data confirmed the noninferiority of incobotulinumtoxinA. Response rates at rest were lower for both products. The rate of adverse events was low.

CONCLUSION IncobotulinumtoxinA is equally as effective as onabotulinumtoxinA in the treatment of glabellar frown lines. Both preparations were well tolerated.

This study was funded by Merz Pharmaceuticals GmbH. Editorial assistance was provided by Ogilvy 4D, Oxford, UK.

Results using a 4 point wrinkle scale

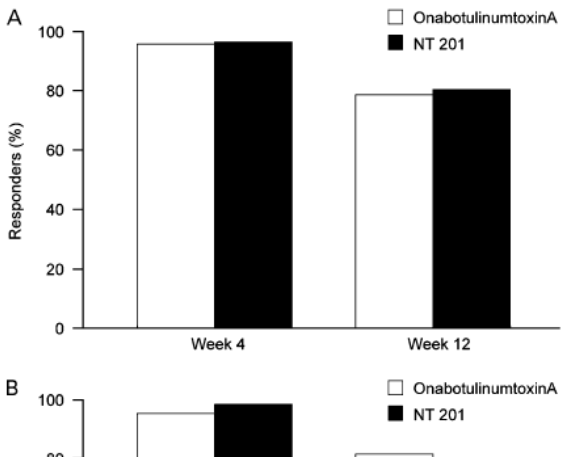

Figure 4. Percentage of responders at maximum frown at weeks 4 and 12 according to the facial wrinkle scale for the per protocol set: (A) independent rater assessment based on digital photographs; (B) investigator assessment based on the live patient.

…but the glabella is just one indication …
the toxins are injected all over the face

Sattler et al. 2011.

- 10 s.U.
- 5 s.U.
- 2-3 s.U.

Dysport U

So we need evidence beyond the glabella!

- 4 BU
- 2 BU
- 0.8 -1.2 BU

Botox / Xeomin U

The first published trial on three facial areas

Efficacy and Safety of IncobotulinumtoxinA in the Treatment of Upper Facial Lines: Results From a Randomized, Double-Blind, Placebo-Controlled, Phase III Study

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BACKGROUND Treating upper facial lines (UFL)—a combination of glabellar frown lines (GFL), horizontal forehead lines (HFL), and lateral periorbital lines (LPL)—is a common aesthetic practice.

OBJECTIVE To provide the first placebo-controlled evidence of the efficacy and safety of incobotulinumtoxinA for UFL.

METHODS Healthy subjects (≥18 years) with moderate-to-severe GFL, HFL, and LPL on the Merz Aesthetics Scales (MAS) at maximum contraction were randomized to incobotulinumtoxinA or placebo. For incobotuli-

strated for investigator-assessed "none" or "mild" scores. Two cases of mild eyelid ptosis occurred with incobotulinumtoxinA.

CONCLUSION IncobotulinumtoxinA demonstrated significant efficacy in treating GFL, HFL, and LPL separately and combined, as well as a good safety profile.

M. Kerscher has received research support and has conducted clinical trials for Merz Pharmaceuticals GmbH (as Head of the Division of Cosmetic Sciences, University of Hamburg, Germany) and has acted as a speaker and/or investigator for Merz, Kythera, Q-Med/Galderma, and Pierre Fabre. B. Rzany has acted as a speaker and/or advisor for IPSEN, Kythera, Merz, Q-Med/Galderma, Teoxane, and Sinclair. W. Prager has acted as a lecturer, advisor, and investigator for Merz, Galderma, and Allergan. P. Trevidic has acted as a speaker for IPSEN, Merz, and Teoxane. C. Inglefield has acted as an advisor and speaker for Merz, Syneron, Eternogen, and Q-Med/Galderma. C. Turnbull has indicated no significant interest with commercial supporters.

So let‘s look at this trial!

Methodology

- prospective
- randomized (2:1)
- double-blind (identical vials)
- placebo-controlled

- multicenter

Indication

- subjects with moderate-to-severe upper facial lines (UFL)

The Crow‘s feet scale at maximum contraction

Flynn et al 2012

Patients were injected based on defined injection points and dosages

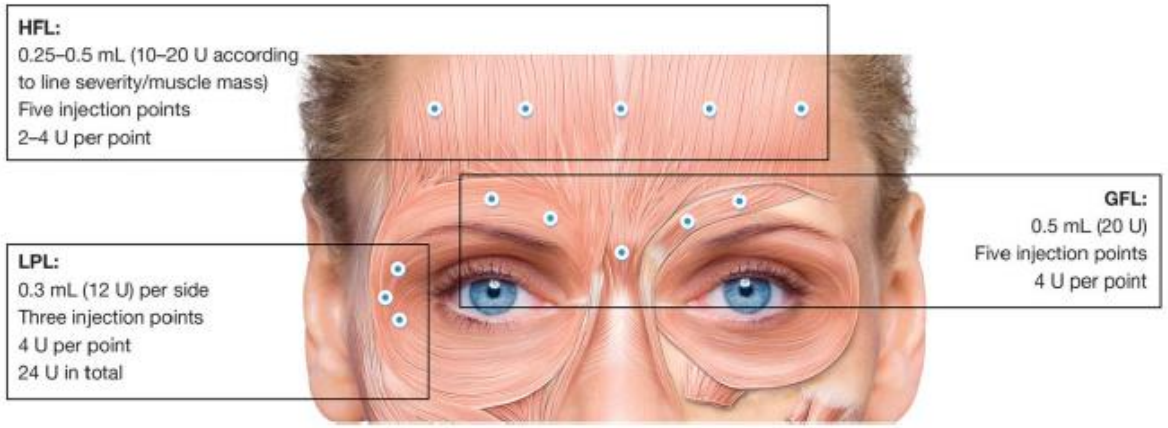


Figure 1. Division of the total administered dose of incobotulinumtoxinA (54–64 U) across the 3 aesthetic treatment areas. Figure reproduced with permission from Merz Pharmaceuticals GmbH.

Kerscher et al. 2015.

There was an exception for the forehead

- For this indication dosing could be adjusted based on muscular activity / grade of elastosis

As a high dosage will result in mostly unwanted moderate to severe brow ptosis

Nestor et al. 2011.

The inclusion and outcome criteria were based on 5-point MAS* scales

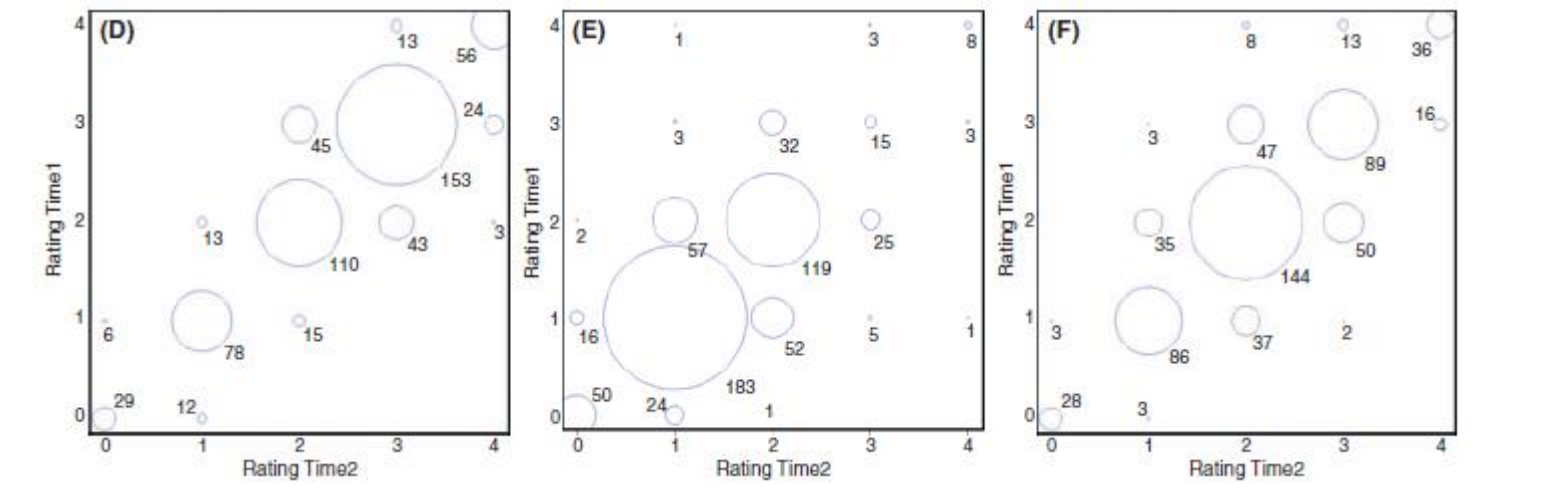
- These are thoroughly validated scales although for most other botulinum toxin studies 4-point scales have been used

* MERZ Aesthetic Scales

The Crow‘s feet scales at maximum contraction

Flynn et al 2012

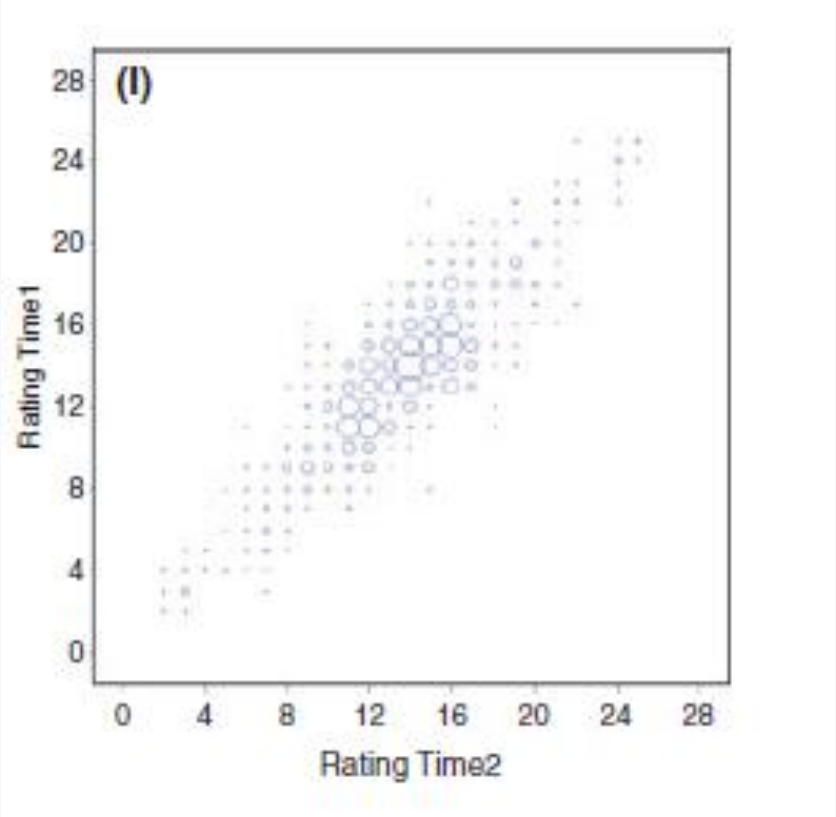
Intra-rater reproducibility single scales upper face



D: Glabella lines dynamic, B: crow‘s feet at rest, C: Crows feet dynamic

Flynn et al 2012

Overall *inter*-rater reproducibility upper face



Flynn et al 2012

Methods
Outcome criteria

- The *primary* efficacy variables comprised
  - the rate of response as calculated by the proportion of investigator- assessed *scores of "none" (0) or "mild" (1) on the 5-point MAS at maximum contraction on Day 30* for each individually treated area (GFL, HFL, and LPL)
  - and also the investigator-assessed combined MAS sum score of #3 at maximum contraction on Day 30 for the 3 treated areas combined (GFL, HFL plus LPL).

Kerscher et al. 2015.

Methods
Outcome criteria

- The *secondary* efficacy variables comprised
  - investigator- and subject-assessed responses on Day 30 for the overall appearance of the upper face according to the clinician's and subject's Global Impression of Change Scale (GICS);

;-)) so these are easier ones to reach

  - investigator- and subject-assessed MMS response of at *least 1-point improvement* from baseline at rest and maximum contraction on Days 8, 30, 60, 90, and 120 for GFL, HFL, and LPL individually
  - ….

Kerscher et al. 2015.

Methods
Study schedule

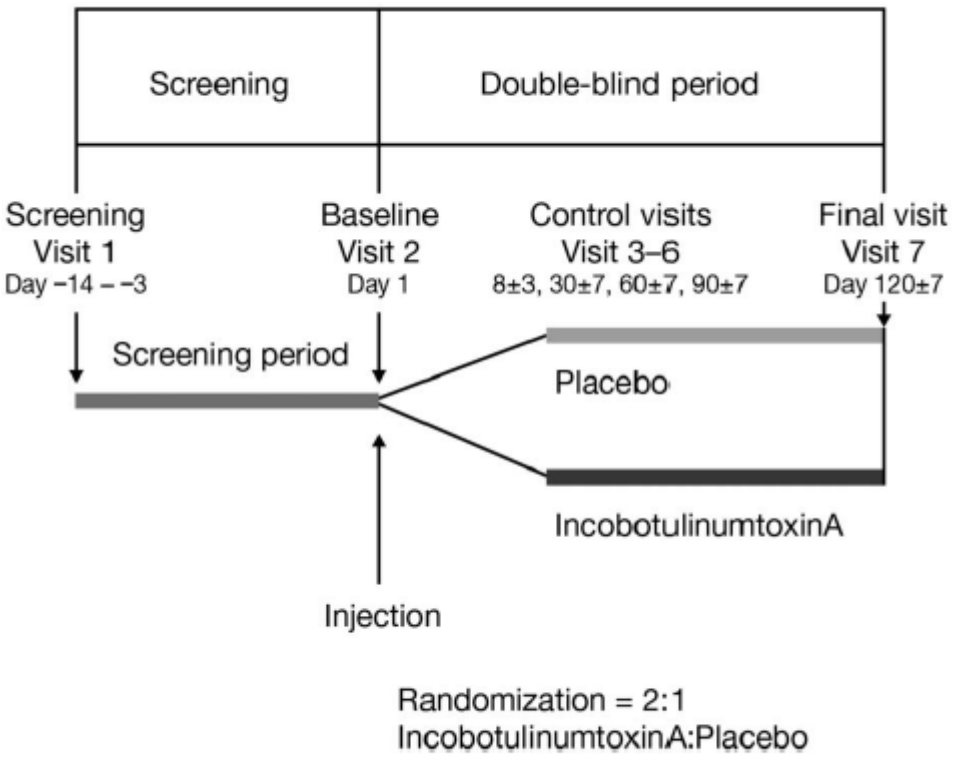


Figure 2. Study assessment schedule.

Kerscher et al. 2015.

Results
Patient flow

Figure 3. Patient flow diagram.

Kerscher et al. 2015.

Results
Main outcome criteria

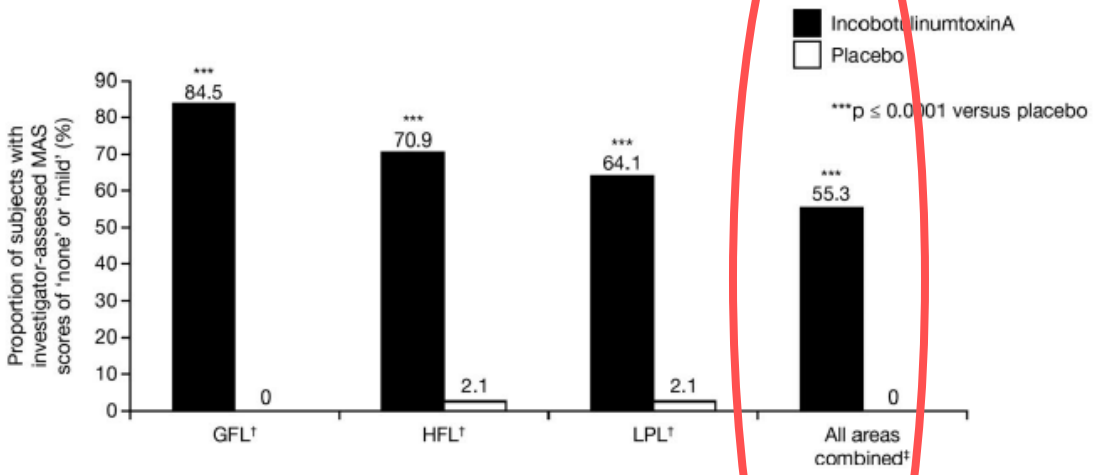


Figure 4. Response rates for investigator-assessed scores of "none" (0) or "mild" (1) on the 5-point MAS for GFL, HFL, and LPL and a sum score of 3 or lower in the UFL combination at maximum contraction on Day 30—observed cases, FAS. †Score of "none" (0) or "mild" (1); ‡sum score of 3 or lower.

Kerscher et al. 2015.

Results

Secondary outcome criteria at day 30

TABLE 3. Proportion of Subjects With a "Much Improved" (Increase of 2 Points) or "Very Much Improved" (Increase of 3 Points) Score on the GICS at Day 30—Observed Cases, FAS

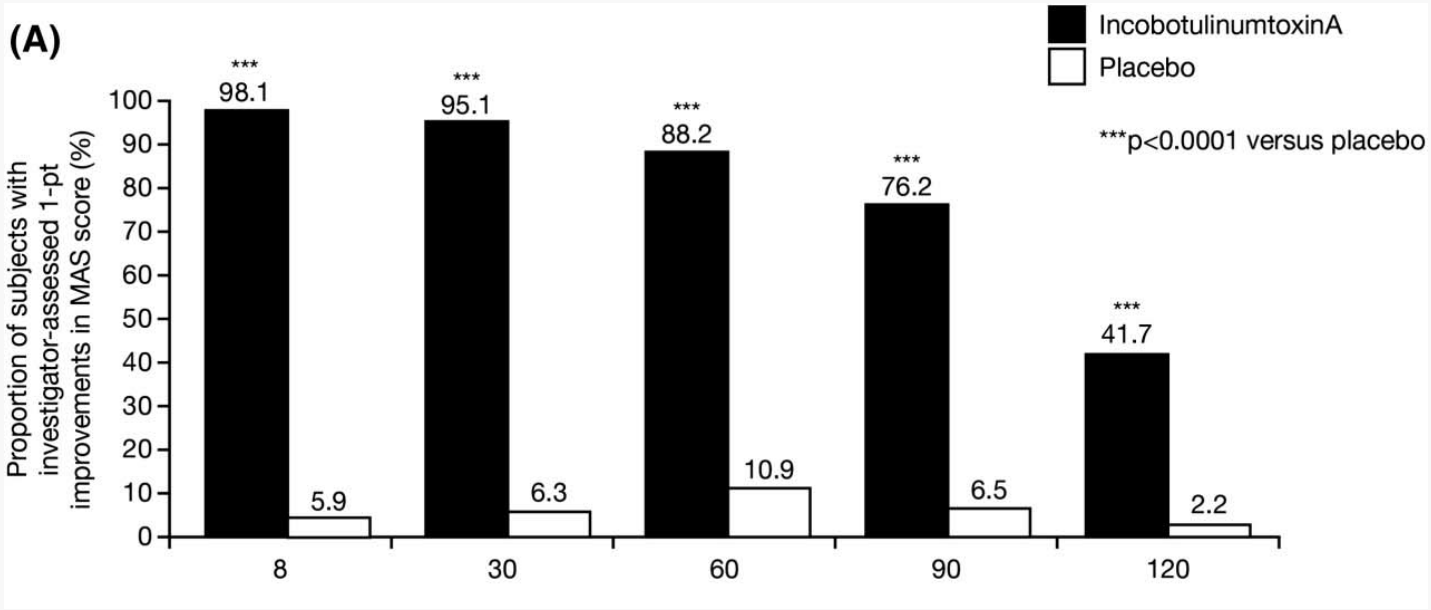
	IncobotulinumtoxinA Group (n = 105) Proportion (%)	*Placebo Group (n = 51) Proportion (%)*	*p* (Logistic Regression Model)
Investigator's rating	86.4	2.1	<.0001
Subject's rating	77.7	2.1	<.0001

Logistic regression model (including investigational site and treatment group as factors) for the treatment area combination (GFL, HFL plus LPL).

Rating according to the GICS: −3 = very much worse; −2 = much worse; −1 = minimally worse; 0 = no change; 1 = minimally improved; 2 = much improved; 3 = very much improved.

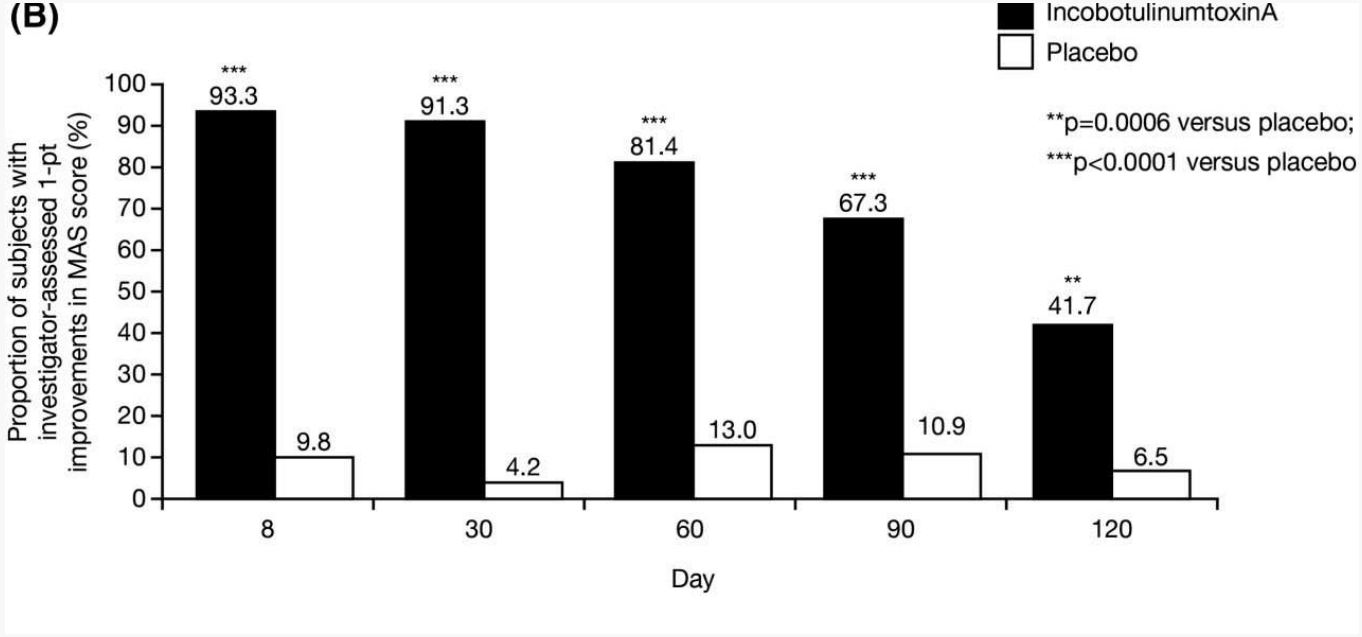
Kerscher et al. 2015.

Results for the glabella
1-point improvement over time
(secondary criteria)



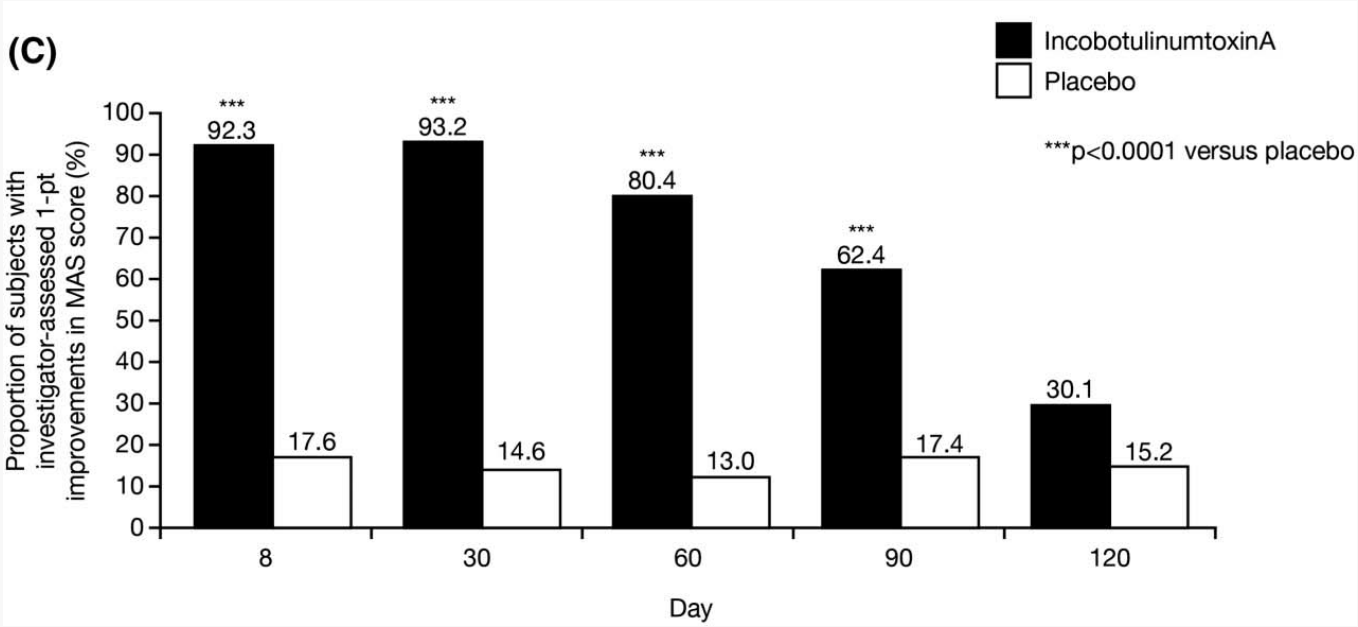
Kerscher et al. 2015.

Results for the forehead
1-point improvement over time
(secondary criteria)



Kerscher et al. 2015.

Results for the crow's feet 1-point improvement over time (secondary criteria)



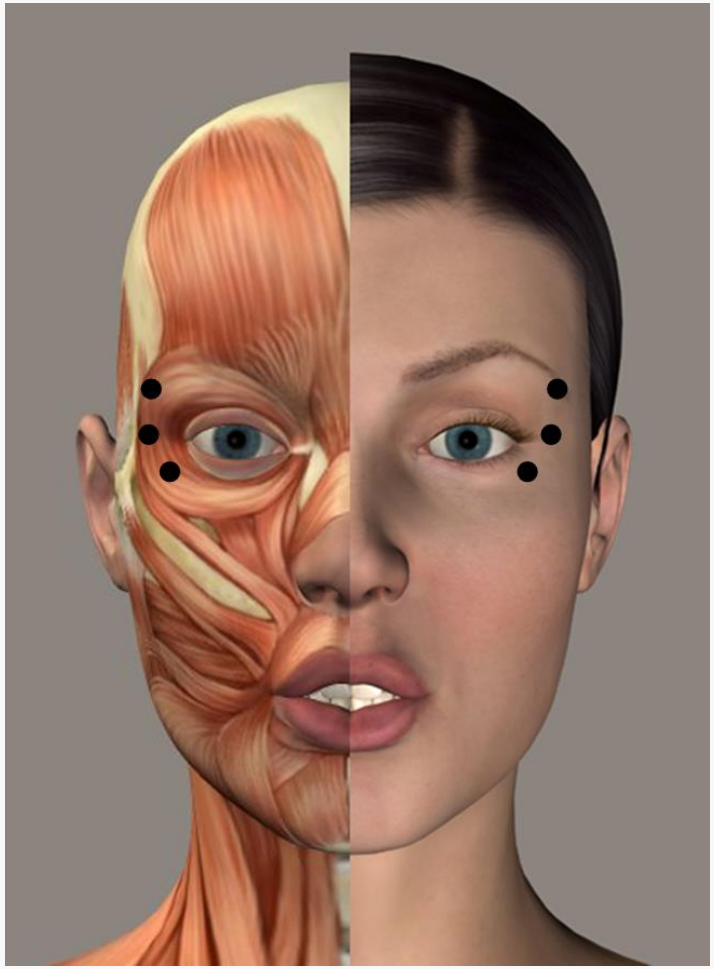
Kerscher et al. 2015.

Summary of efficacy

- Efficacy was good for all indications – but a bit weaker for the crow's feet

What are the reasons for that?

- The zygomatic muscles, e.g. the smile is determined not only by the m. orbicularis oculi but by other muscles, too



De Maio and Rzany 2007.

Results
Safety

- Treatment-emergent AEs of special interest
  - 2 cases of eyelid ptosis*, with one case being unilateral and the other being bilateral (n = 2; 1.9%), and 2 cases of dry eyes (n = 2; 1.9%).

*Both incidences of eyelid ptosis were considered to be mild

Kerscher et al. 2015.

What was a challenge of this trial!

- A very high proportion of screening failures!

Results
Patient flow

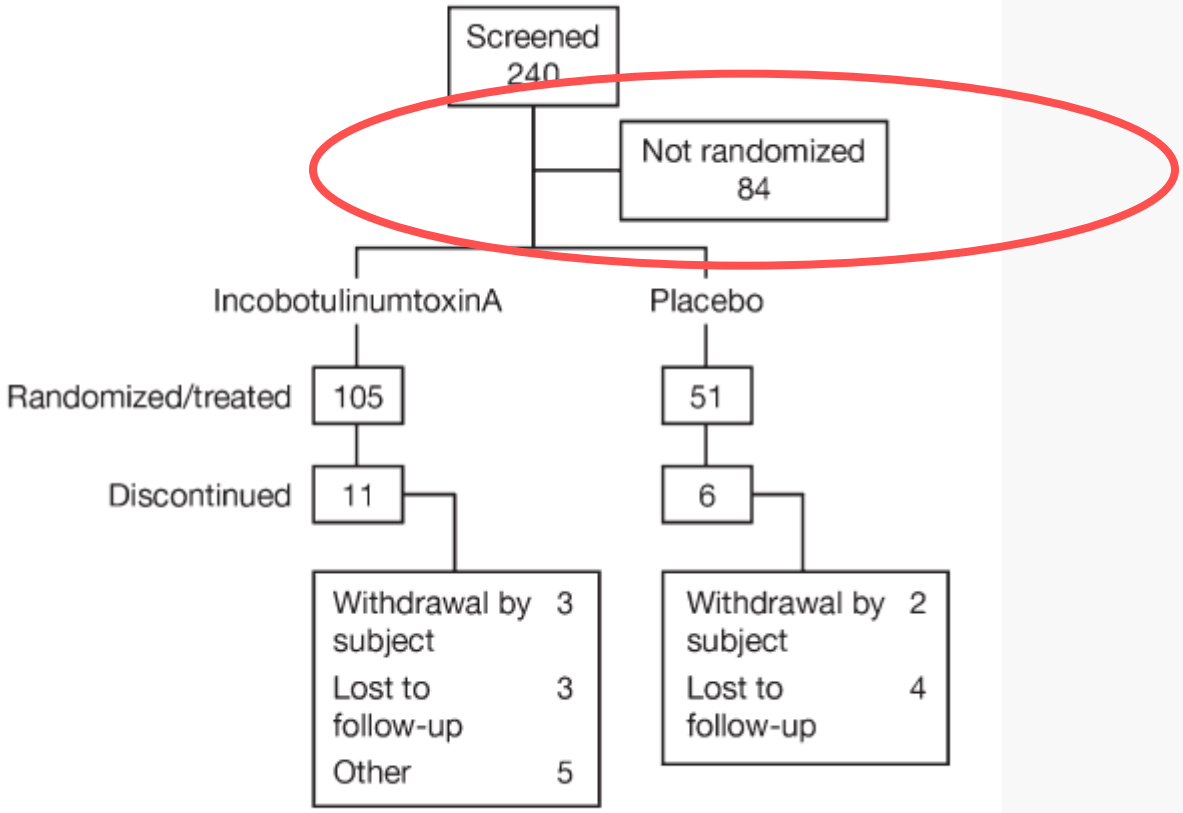


Figure 3. Patient flow diagram.

Kerscher et al. 2015.

Reason for screening failure

- Patients failed the questionnaire for significant psychological impact (FLQA-k)

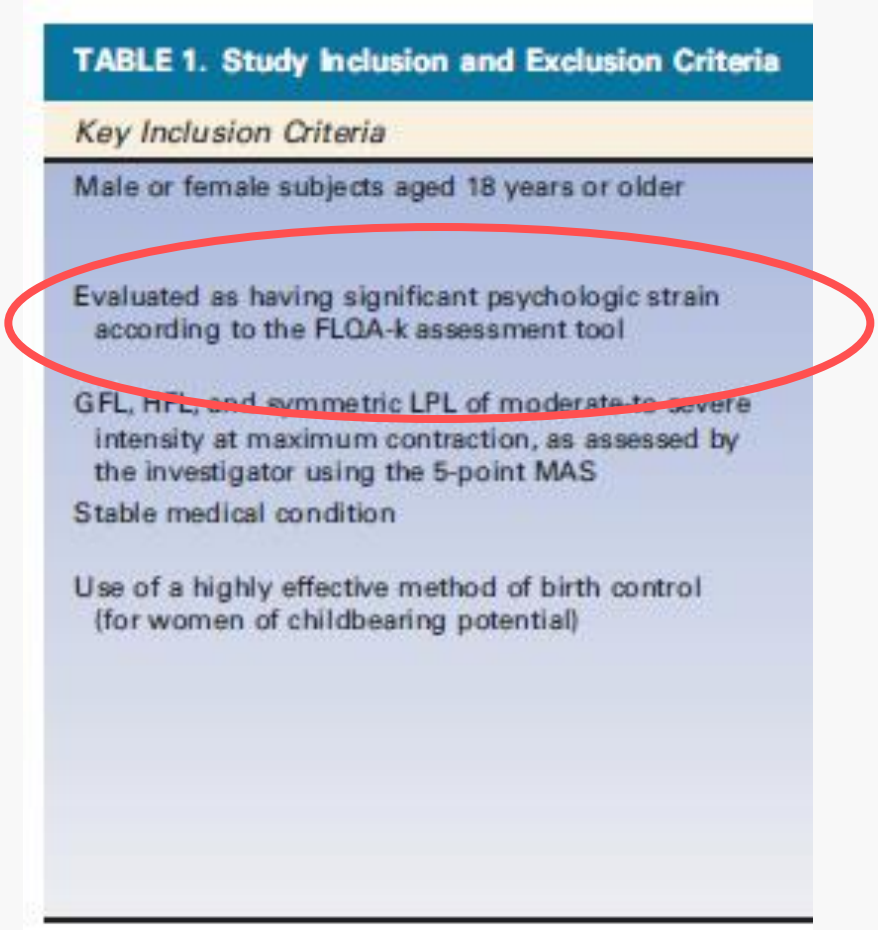


TABLE 1. Study Inclusion and Exclusion Criteria

Key Inclusion Criteria

Male or female subjects aged 18 years or older

Evaluated as having significant psychologic strain according to the FLQA-k assessment tool

GFL, HFL, and symmetric LPL of moderate to severe intensity at maximum contraction, as assessed by the investigator using the 5-point MAS

Stable medical condition

Use of a highly effective method of birth control (for women of childbearing potential)

What is the FLQA-k?

- The FLQA-k is a patient-reported outcome tool for the evaluation of self-perception of a subject's body and aesthetic appearance. The questionnaire

There are no published references for this tool and it had been never used before in an RCT

significant psychologic strain.

So why was it used!

- Because of *regulatory* reasons
  - The inability of the German BfArM to accept that botulinum toxin is used beyond a clear disease definition

Summary

- Incobotulinumtoxin A proved to be efficacious and safe when treating three adjacent facial areas at the same time

Summary

- This study adds important evidence to the use of BoNT-A for this commonly used aesthetic indications

Summary

- The study is less comparable to other botulinum toxin studies because of several reasons
  - Outcome criteria: a 5 point score was used instead of a 4 point score
  - Inclusion criteria: by using a questionnaire as an inclusion criteria that deselected patients otherwise deemed fit to be treated

Summary

- The FLQA-k questionnaire was added because of the pressure of the German agency
- This made the study less comparable to other studies and more expensive due to the high number of unnecessary screening failures

Which raises the questions ….

Does this reflect real ethic concerns of the agency or is this more bigotry/paternalism towards aesthetic medicine?

;-)) and who controls the agency!