



Recent developments in clinical trials of botulinum neurotoxins



Antoniangela Cocco ^a, Alberto Albanese ^{a, b, *}

^a Humanitas Research Hospital, Rozzano, Milano, Italy

^b Catholic University, Milano, Italy

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ABSTRACT

Botulinum neurotoxins (BoNTs) are increasingly used in clinical practice for several indications. Following the pioneering years of discoveries, the recent years have witnessed an increase of new indications and new toxin brands.

We review here the clinical trials on BoNTs performed since 2014 and put them into perspective. We also review the ongoing trials listed by the National Institutes of Health registry (ClinicalTrials.gov). The following indications are reviewed here: blepharospasm, cervical dystonia, spasticity, cerebral palsy, urinary incontinence, headache, topical formulations, postoperative cardiac arrhythmia, keloids and scars. For each of these indications the latest trials are reviewed and commented.

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1. Introduction

Botulinum neurotoxins (BoNTs) are being increasingly used in clinical practice since the 1970s. Originally, BoNT/A was developed for ophthalmological indications by Alan Scott, under an Investigational New Drug license for the treatment of strabismus granted by the FDA. Few years later, based on the interest of English ophthalmologists based at Moorfields eye hospital, the Center for Applied Microbiology and Research (CAMR) at Porton Down formed a partnership with a biotechnology company called Porton International and developed the second BoNT/A product Dysport (DYS-tonia PORTon Down). Later two other toxin brands were developed, one containing BoNT/B (NeuroBloc/MyoBloc) and one being another type of BoNT/A without complexing proteins (Xeomin). BoNT/A products proved to be effective in a range of extraocular conditions, such as dystonia syndromes (blepharospasm, hemifacial spasm, cervical dystonia, Meige syndrome, oromandibular dystonia, and writer's cramp), spasticity and others. Currently, in most western

countries the following BoNT products are branded: three BoNT/A (onabotulinumtoxinA or Botox[®], abobotulinumtoxinB or Dysport[®], incobotulinumtoxinA or Xeomin[®]) and one BoNT/B (rimabotulinumtoxinB or NeuroBloc[®]/Myobloc[®]). Additional trade names are also used for these toxins and other toxin brands are produced in Korea, China, and USA with a variety of names ([Table 1](#)).

We performed a review of all the clinical trials published during the last three years and of the unpublished trials to provide updated information on the recent developments of BoNT. Published studies were retrieved from the Medline database via PubMed; unpublished studies were retrieved by searching ClinicalTrials.gov. In addition, articles related to BoNT mechanism of action and usage were taken into consideration when relevant. Searches were concluded in May 2017. We summarize hereafter the recent advances achieved during recent years (since 2014).

It has been demonstrated that BoNT/A, BoNT/D, and TeNT enter neurons via two separate entry pathways, an established synaptic vesicle recycling pathway that leads to local effects and a distinct secondary uptake pathway that directs these toxins to a common, non-acidified, retrograde carrier ([Bomba-Warczak et al., 2016](#)). This secondary pathway leads to distal effects in neurons upstream from the cells that mediate the initial uptake of these agents. The central action of BoNT is pivotal for understanding the action of BoNTs in several neurological conditions, such as dystonia, spasticity and pain. Recent partially published data also support a role of BoNT in neural plasticity both centrally and peripherally. The recent evidence on the central effects of BoNTs is reviewed in this issue ([Restani and Caleo, 2017](#)).

Abbreviations: AE, Adverse event; BoNT, Botulinum neurotoxin; CD, Cervical dystonia; CGRP, calcitonin gene-related peptide; CP, cerebral palsy; IGA, Investigator's Global Assessment; IL-6, Interleukin 6; MMP-1, Matrix metalloproteinase-1; PDGFA, Platelet Derived Growth Factor Subunit A; TeNT, Tetanus NeuroToxin; TGF-β1, Transforming growth factor beta 1; VEGF, Vascular endothelial growth factor; VIP, vasoactive intestinal peptide.

* Corresponding author. Humanitas Research Hospital, Via A. Manzoni 56, 20086, Rozzano, Milano, Italy.

E-mail address: alberto.albanese@unicatt.it (A. Albanese).

Table 1
Marketed BoNT products.

Brand name	FDA generic name	Manufacturer	Country
Botox, Vistabel, Vistabex, Botox Cosmetic	onabotulinumtoxinA	Allergan	USA
Dysport, Reloxin, Dysport Cosmetic	abobotulinumtoxinA	Ipsen	UK France
Xeomin	incobotulinumtoxinA	Merz	Germany
Myobloc, Neurobloc	rimabotulinumtoxinB	Solstice	USA
Neuronox, Botulif, Cunox, KbtxA, Meditoxin, Neuramis, Siax, MT 10107, MT 10109, Meditoxin injection - Medy-Tox		Medytox	Korea
Prosigne, BTX-A, CBTX-A, Hengli, Lantox		Lanzhou Biological Products	China
Botulax		Hugel	Korea
PurTox		Mentor Corporation	USA
Nabota, DWP-450, Evosyal		Daewoong Pharmaceutical	Korea

AbbreviationsFDA: Food and Drug Administration.

2. Headache

OnaBoNT/A was approved in 2010 by the FDA for the prophylactic treatment of chronic migraine. Approval was granted based on two phase III trials, called PREEMPT (Phase III REsearch Evaluating Migraine Prophylaxis Therapy). The PREEMPT 1 trial showed no significant efficacy of onaBoNT/A for headache episodes (primary endpoint), but a significant improvement of headache days and migraine days (secondary endpoints) (Aurora et al., 2010). The PREEMPT 2 trial reported a reduction of headache days per 28 days relative to baseline (Diener et al., 2010). Recently, data from the two PREEMPT cohorts were pooled into a post hoc analysis assessing the proportion of study patients who achieved a $\geq 50\%$ reduction in headache days (Silberstein et al., 2015). This analysis showed that a meaningful proportion of patients with chronic migraine, who did not respond to the first or second onaBoNT/A injection cycle, improved after subsequent treatment cycles, indicating that response to BoNT treatment may occur after a first cycle apparently failed to provide improvement.

The recent guidelines published by the American Academy of Neurology established a grade A recommendation (should be offered) for onaBoNT/A in chronic migraine and considered it ineffective (should not be offered) for episodic migraine (Simpson et al., 2016). The recent pragmatic data on headache management are reviewed in this issue (Green and Rothrock, 2017; Tassorelli et al., 2017).

Recent research has also focused on the levels of calcitonin gene-related peptide (CGRP), which are considered biomarkers of migraine (Durham, 2008). A pilot study measured CGRP in patients with chronic migraine comparing onaBoNT/A to placebo (Cady et al., 2014). OnaBoNT/A caused a greater reduction of CGRP levels than placebo, a non-significant difference. Another trial measured CGRP and vasoactive intestinal peptide (VIP) levels in blood samples of 81 patients with chronic migraine prior to and after treatment with onaBoNT/A. Patients with higher levels of CGRP and VIP were the most responsive to onaBoNT/A treatment (Cernuda-Morollon et al., 2014). These data were confirmed by another study conducted by the same research group (Cernuda-Morollon et al., 2015). They represent an initial attempt to determine which factors could predict a clinical response to BoNT/A, to find predictors of clinical outcome and subgroup markers.

3. Blepharospasm

Blepharospasm is a focal dystonia that results in hyperactivity of periocular muscles. Although BoNT is the most effective treatment for blepharospasm, there is a small portion of patients who report unsatisfactory responses. Various injections technique have been advocated to optimize response to BoNT. Injections are generally placed in the orbital or in the pretarsal portions of the orbicularis

oculi, the latter especially if the so-called “apraxia of eyelid opening” coexists. A recent study confirmed that combined, orbital and pretarsal, injections may be useful in patients who do not respond to orbital injections (Esposito et al., 2014), thus supporting historical observations that pretarsal injections can provide optimal results also in classic blepharospasm, especially if a patient was previously unresponsive (Albanese et al., 1996).

The recently released AAN guidelines considered onaBoNT/A and incoBoNT/A as probably effective (Level B) and aboBoNT/A as possibly effective (level C) for the treatment of blepharospasm (Simpson et al., 2016). Given the long-standing evidence on efficacy of BoNT in blepharospasm, these recommendations reflect the quality of published studies, many of which belong to the pioneering BoNT era.

A controlled clinical trial compared incoBoNT/A and onaBoNT/A in 48 patients, using a split technique: each patient was treated with both toxins, each one on either side. The study showed no difference, in duration time or efficacy (Saad and Gourdeau, 2014).

4. Cervical dystonia

All marketed BoNT products are licensed for use in cervical dystonia (CD). Their efficacy has been supported by a wealth of data dating back to the 1980s and has been confirmed by the recent AAN guidelines (Simpson et al., 2016), where the four BoNT products marketed in the USA were, for the first time, reviewed as individual drugs. The result of this exercise was somehow a paradox: only aboBoNT/A and rimaBoNT/B were established as effective in CD (class A evidence), whereas onaBoNT/A and incoBoNT/A were considered as probably effective (class B) (Albanese, 2016).

Recent controlled clinical trials on CD have mainly focused on the comparison between different toxin brands. OnaBoNT/A and aboBoNT/A were compared in two randomized, double-blind, crossover studies. In a first trial, 46 patients were randomized, at two different ratios of proprietary units (1:3 or 1:1.7), to treatment with onaBoNT/A or aboBoNT/A. As assessed by the TWSTRS score four weeks after treatment, the two products showed similar efficacy at each ratio (Rystedt et al., 2015); however, 12 weeks after treatment there was a greater efficacy of aboBoNT/A at the 1:3 ratio. In a second study, 94 patients completed the randomization and then the crossover switch between onaBoNT/A and aboBoNT/A at a 1:2.5 dose ratio (Yun et al., 2015). There were no differences in the efficacy measures, which included: Tsui scale, TWSTRS, proportion of improvement in clinical global impression and patient global impression. These recent data did not therefore allow defining unequivocally a conversion rate between proprietary units of aboBoNT/A and onaBoNT/A for CD.

A prospective, randomized, double blind trial on 34 patients explored the efficacy of Lanzhou BoNT/A (Prosigne®) compared to aboBoNT/A, using a 1:3 ratio (Barbosa et al., 2015). The mean

TWSTRS score was similar for both formulations after the last injection. The proportion of patients who experienced adverse effects was similar in both treatment groups, with dysphagia being the most frequent adverse event (27.27%), followed by pain at the injection site (4.54%) and muscle weakness (1.3%). This study was in keeping with an earlier trial evaluating the efficacy of Prosigne in patients with CD (Quagliato et al., 2010). However, further larger studies are required to confirm the efficacy and safety of this toxin in CD.

A non-controlled cross over study compared the efficacy and the duration of therapeutic effect of onaBoNT/A and incoBoNT/A in 40 patients. They were injected for at least four cycles with one toxin and then switched to the other, using a 1:1 conversion ratio. There were no significant differences in efficacy between the two groups (Dressler et al., 2014).

Non-responsiveness to BoNT injections is one of the main challenges in the clinical management of CD. Lack or decrease in magnitude of response can be observed after the first BoNT/A cycle (so-called primary non-responding patients), or after later treatment cycles (secondary non-responders). A retrospective study tried to shed light on which factors can predict secondary non-response in patients with idiopathic CD (Ferreira et al., 2015). Fifty-two patients with insufficient improvement of dystonic postures after ≥ 3 unsuccessful injection cycles were selected. A multivariate conditional regression analysis showed that the main predictors of secondary non-response were a previous recourse to other therapies (such as neuroleptic use or surgical procedure), a higher number of serious treatment-related AEs, more frequent interruptions of BoNT/A treatment and higher median BoNT/A doses. This study suggested that – aside the common belief that inappropriate muscle selection is the main cause (Nijmeijer et al., 2013) – secondary non-response is also related to underlying disease severity.

Efficacy of BoNT may be considered unsatisfactory by the patient or the doctor. A prospective study evaluated 35 patients with CD, whose response to BoNT/A was considered unsatisfactory by the treating specialist (Jinnah et al., 2016). Patients had an average duration of illness of 12.5 years; approximately half of them received polyEMG to identify the pattern of muscle activation. The main causes of treatment failure were: suboptimal dosage, wrong muscle targeting, complex CD subtype. The reasons for unresponsiveness were also reviewed by another center reporting similar causes of unsatisfactory outcome (Erro et al., 2016). There is general agreement that polyEMG may facilitate muscle selection, thus improving outcome (Erro et al., 2016; Nijmeijer et al., 2013), although this point still remains debated (Jinnah and Factor, 2016).

5. Spasticity and cerebral palsy

The recently published AAN guidelines provide class A evidence (should be offered) to onaBoNT/A and aboBoNT/A for the treatment of upper and lower limb spasticity (Simpson et al., 2016). Instead, incoBoNT/A received class A evidence and rimaBoNT/B class B evidence (should be considered) only for upper limb spasticity. This classification reflects the number and quality of available studies, rather than the therapeutic potential of each BoNT brand.

The use of recommended assessment scales is crucial to determine the outcome of clinical studies. When used as outcome measures, rating scales should reliably measure the efficacy of a treatment on the various components of the disease and, at the same time, they should respond to rigorous clinical standards (Aaronson et al., 2002). Most clinical trials that evaluate BoNTs in spasticity used the Ashworth scale (or its modified version) as primary outcome. Although this is considered a useful and simple tool to estimate the physical sign of spasticity, some authors raised

the doubt that some clinically relevant aspects are not adequately captured by this rating tool (Gracies et al., 2015). In particular, rating scales assessing function should also be used as primary outcome measures, considering that spasticity reduction is a starting point along the path of rehabilitation (Elia et al., 2009).

6. Safety issues in children

In 2008, the safety of BoNT for children with cerebral palsy (CP) was called into question by the US Consumer Advocacy Group Public Citizen, which petitioned the US Federal Drug Administration to increase label warnings for commercially available BoNT/A products. Concerns about the safety of BoNT had been raised especially after 2005, when an analysis of the US Food and Drug Administration related 28 deaths to BoNT treatment (Cote et al., 2005). Recently, Vigibase, the World Health Organization global individual case safety report (ICSR) database, was reviewed with the aim to examine the safety of BoNT/A treatment in the pediatric population using a disproportionality analysis (Montastruc et al., 2017). One hundred and sixty-two individual case safety reports (ICSR), involving children aged 1–17 years with spasticity, were retrieved: 109 of them (67%) had serious adverse effect (AE). The most frequently reported AEs were dysphagia (including aspiration), followed by asthenia/fatigue and muscular weakness. Death was reported in 19 cases, mainly due to pneumonia and botulism. The main mechanisms identified were: the spread of BoNT beyond the injection site, coincident treatment with sedative drugs and a severe underlying disease.

During the 2014–2017 period, several controlled clinical trials investigated the occurrence of AEs in CP. A controlled clinical trial evaluated the incidence of AEs in 41 children randomized to either a BoNT/A cycle or to sham injections. Subsequently, both groups underwent a BoNT/A injection cycle. There were no differences in the rates of moderate or serious AEs between the two groups in the first part of the study (Edwards et al., 2015). Two other trials assessed the efficacy and safety of incoBoNT/A (Carraro et al., 2016) and aboBoNT/A (Delgado et al., 2016) respectively, in children with lower limb spasticity associated with CP. Mild or moderate AEs such as pyrexia, local muscular weakness, fatigue, pain, sleepiness and gait abnormalities were reported in both studies. No severe AEs, resulting in death or requiring hospitalization, were noticed in one study, while the other reported some serious AEs, mostly in the placebo group.

These data provide a notable discrepancy in the incidence of AEs in clinical trials compared to the pharmacovigilance databases. This may be resolved by considering the difference between real life clinical practice (reported in registries) and specialized practice (expressed in trials). Not all centers performing BoNT injections have expertise on dose selection for complex cases, perform targeting with ultrasound or EMG guidance, take action to substantially limit the systemic spread or local diffusion of BoNT. This suggests that guidance should be mandatory, particularly in children, and certification of centers may be required for some specialized practice.

Recent evidence furthermore confirms that BoNT/A injections can be combined with occupational therapy, an association providing improved bimanual performance in children with CP (Lidman et al., 2015).

7. Urinary incontinence

A novel formulation developed for the treatment of patients with overactive bladder is liposome-encapsulated onabotulinumtoxinA. This formulation uses liposomes (LPs) as a vehicle for administering BoNT, due to the permeability of bladder urothelium.

This conformation allows to perform intravesical administration without need of injections. In a pilot clinical trial, 24 patients were randomized to lipotoxin (80 mg liposomes and 200 U aboBoNT/A) or placebo (Kuo et al., 2014). An improvement of the average frequency and urgency of episodes, but not of urinary urgency or incontinence, was observed after lipotoxin treatment (Kuo et al., 2014). In a multicenter, randomized, double-blind study, 62 patients with overactive bladder were randomized to receive instillation of 200 U of onaBoNT/A and 80 mg sphingomyelin liposome, or saline (Chuang et al., 2014). They experienced 1 or more urinary urgency incontinence episodes per day and had a mean micturition frequency of ≥ 8 episodes at baseline. Four weeks after treatment liposomal BoNT/A decreased the micturition frequency to 3/day and improved other secondary study endpoints. However, no conclusion was drawn regarding urinary urge incontinence episodes that were not common at baseline. No urinary retention or increase in post-void residual urine volume were observed (Chuang et al., 2014).

The evidence collected suggests that liposome-encapsulated BoNT/A may effectively improve frequency and urgency in patients with overactive bladder. The penetration of lipotoxin to the urothelium may be limited and may lack a direct effect on the detrusor. Clinical action is probably mediated by a blockage of muscarinic receptors and afferent nervous pathways associated with a consequent reduction of central sensitization. Lipotoxin instillation appears safe and with less adverse effects than direct BoNT/A injection, but shorter duration. Further trials comparing Lipotoxin with other treatments are needed to confirm the role of Lipo-BoNT/A in the management of overactive bladder. A first answer may possibly come from an ongoing controlled trial comparing Lipotoxin to onaBoNT/A for the treatment of interstitial cystitis (NCT02247557). Unpublished and ongoing clinical trials on liposome encapsulated BoNT/A are listed in Table 2.

The positioning of BoNT/A treatment compared to more invasive procedures, such as sacral neuromodulation, has been the object of recent studies. A recent multicenter open-label randomized controlled study on 381 women with refractory urinary urgency-incontinence reported that BoNT injections were more efficacious than sacral neuromodulation to reduce daily episodes of urgency incontinence after 6 months (Amundsen et al., 2016). Moreover, 20% of patients in the onaBoNT/A group had a complete resolution of urgency-incontinence, compared to only 4% in the sacral neuromodulation group. In clinical practice, however, the choice between these two alternative treatments is still not obvious, particularly considering that no significant differences were observed in quality of life parameters, subjective preference, convenience, or adverse effects. Furthermore, patients in the BoNT/A injections group frequently presented urinary tract infections and needed self-catheterizations.

8. Topical formulations

The possibility to produce topical formulations of BoNTs is an

attractive innovation that has not yet been commercially developed. Topical BoNT may theoretically be employed in patients with needle phobia or in patients with hyperhidrosis, where multiple painful BoNT injections are required (Campanati et al., 2013). Although attractive, this line of development has not been very successful so far, with many registered and still unpublished studies dating back several years.

DaxibotulinumtoxinA (RT001) is a topical gel containing a purified 150-kDa daxiBoNT/A combined with a peptide and a poloxamer diluent. In a pilot study on 12 patients with primary axillary hyperhidrosis sweat production was reduced over a 4-week period (Glogau, 2007). The efficacy and safety of RT001 for the treatment of lateral canthal lines was explored in two controlled trials (Brandt et al., 2010; Glogau et al., 2012). Currently, there are 10 registered clinical trials evaluating the efficacy of RT001 in the treatment of severe several canthal lines (NCT01776606, NCT01940991, NCT01064518, NCT01124552, NCT00968825, NCT00968942, NCT00888914, NCT00907387, NCT00884234 and NCT02580370) and one controlled clinical trial to assess the reduction of sweating in patient with axillary hyperhidrosis (NCT02565732). These studies have been completed, but the results are not yet available; furthermore, Revance (the study sponsor) has recently communicated failure of the REALISE 1 trial (NCT02580370) on the topical administration of RT001 for canthal lines and the decision to discontinue drug development (Herbert, 2016).

Cosmetox is a topical product consisting of BoNT/A stabilized by other molecules with nanoparticle technology to enhance skin absorption. A controlled clinical trial, evaluated the efficacy of Cosmetox compared to placebo cream for the treatment of hyperkinetic lines (Chajchir et al., 2008). There are currently no registered clinical trials evaluating the efficacy of this topical product.

A third topical product is under development by Anterios Inc (Allergan) with different denominations (ANT1207, ANT1401, ANT1403). No controlled clinical trials have been published yet, but three ongoing studies are registered to evaluate its cosmetic potential on lateral canthal lines (NCT01358695, NCT01951742, NCT01809964). A pilot trial to evaluate the efficacy of ANT1207 in patients with acne (NCT01293552), and two studies on axillary hyperhidrosis (NCT02479139, NCT01799824) are also underway.

Unpublished and ongoing clinical trials on topical BoNTs are listed in Table 3.

9. New and emerging indications

Pathophysiological mechanisms underlying atrial fibrillation include sympathetic and parasympathetic denervation supersensitivity. These fibers are mainly located in the pericardial fat tissue. Several studies have shown that ablation of the epicardial fat pad can yield to a greater electrical homogeneity and reduce the incident of atrial fibrillation, the most common complication after cardiac surgery, especially in the first week after the operation.

Injection of incoBoNT/A into the major epicardial fat pads have been shown to be safe and efficacious to prevent atrial fibrillation in

Table 2
Unpublished and ongoing clinical trials on liposome encapsulated BoNT/A (source: [Clinicaltrials.gov](https://clinicaltrials.gov)).

Study	Compound	N° of patients	Trial Design	Follow up	Outcome Measures	Results/status
NCT02247557	Liposome encapsulated BoNT/A and onaBoNT/A	90	Randomized, double-blind, placebo controlled	1 month after the treatment day	Primary: Change of the O'Leary-Sant symptom score Secondary: Visual Analog Scale (VAS), functional bladder capacity (FBC) voiding frequency at daytime and at night time as recorded in 3-day voiding diary, Global response assessment (GRA), maximum flow rate, PVR from baseline to 1 month after the treatment day, urinary nerve growth factor, Changes of cytokines level	Completed; no study results posted

Table 3Unpublished and ongoing clinical trials on topical botulinum toxin (source: [Clinicaltrials.gov](https://clinicaltrials.gov)).

Study	Compound, Producer	Trial Design *	Indication	Duration	Outcome measures	Results/status
NCT01776606	DaxibotulinumA topical gel (RT001), Revance	Randomized, double-blind, placebo controlled	Lateral canthal lines	Week 4 Week 4	Primary: Composite endpoint based upon the IGA and patient assessment of severity of lateral canthal lines. Secondary: Proportion of subjects with 2 point or greater improvement from baseline using the IGA; Proportion of subjects with 1 point or greater improvement from baseline using the IGA; Proportion of subjects with a 2 point or greater improvement from baseline using the SSA	Completed; no study results posted
NCT01940991	DaxibotulinumA topical gel (RT001), Revance	Randomized, double-blind, placebo controlled	Severe Crow's Feet Lines	=	=	Completed; no study results posted
NCT01064518	DaxibotulinumA topical gel (RT001), Revance	Randomized, double-blind, placebo controlled	Lateral Canthal Lines	Week 4 Week 8	Primary: improvement based on the investigator global and patient assessments. Secondary: improvement based on the investigator global and patient assessments.	Completed; no study results posted
NCT01124552	DaxibotulinumA topical gel (RT001), Revance	Randomized, double-blind, placebo controlled	Moderate to Severe Lateral Canthal Lines	Week 4 Week 4	Primary: Subject improvement based on the IGA Secondary: Subject Improvement and number of subjects based on investigator and patient assessments.	Completed; no study results posted
NCT00968825	DaxibotulinumA topical gel (RT001), Revance	Randomized, double-blind, placebo controlled	Moderate to Severe Lateral Canthal Lines	Week 4 Week 4 and 6	Primary: The number of subjects classified as exhibiting improvement via the IGA of Lateral Canthal Line Severity at Rest; incidence of treatment emergent AEs Secondary Outcome Measures: The number of subjects classified as exhibiting improvement via the IGA of Lateral Canthal Line Severity at Rest and Smile; incidence of treatment emergent AEs	Completed; no study results posted
NCT00968942	DaxibotulinumA topical gel (RT001), Revance	Randomized, double-blind, placebo controlled	Moderate to Severe Lateral Canthal Lines	Week 8 Weeks 2, 4, 6, 8	Primary: The number of subjects classified as exhibiting improvement via the IGA of Lateral Canthal Line- Rest Severity Scale of the LCA; incidence of treatment emergent AEs Secondary: The number of subjects classified as exhibiting improvement via the Investigator Global Assessment at Rest; Incidence of treatment-emergent AEs	Completed; no study results posted
NCT00888914	DaxibotulinumA topical gel (RT001), Revance	Randomized, double-blind, placebo controlled	Moderate to Severe Lateral Canthal Lines	Day 28 Day 28	Primary: The number of subjects classified as exhibiting improvement via the Investigator Global Assessment at Smile Secondary: The number of subjects classified as exhibiting improvement via the Investigator Global Assessment at Rest; Incidence of treatment-emergent AEs	Completed; no study results posted
NCT00907387	DaxibotulinumA topical gel (RT001), Revance	Randomized, double-blind, placebo controlled	Moderate to Severe Lateral Canthal Lines	Day 28 Day 28	Primary: The number of subjects classified as exhibiting improvement via the IGA at Rest Secondary: Incidence of treatment-emergent adverse events	Completed; no study results posted
NCT00884234	DaxibotulinumA topical gel (RT001), Revance	Randomized, double-blind, placebo controlled	Moderate to Severe Lateral Canthal Lines	Week 6	Primary Outcome Measures: The number of subjects classified as exhibiting improvement via the Investigator Global Assessment from Baseline to End of Study; Incidence of treatment emergent AEs.	Completed; no study results posted
NCT02580370	DaxibotulinumA topical gel (RT001), Revance	Randomized, double-blind, placebo controlled	Lateral Canthal Lines	Week 4 Week 4	Primary: Composite endpoint based upon IGA and PSA Secondary: IGA with 2 points or greater improvement from baseline; IGA with 1 point or greater improvement from baseline; patient Severity Assessment with 2 points or greater improvement from baseline; Proportion of subjects with a 1 point or greater improvement from baseline using the Patient Severity Assessment	Completed; no study results posted
NCT01358695	ANT-1207	Randomized, double-blind, placebo controlled	Lateral Canthal Lines		Primary: IGA Score. Wrinkle scale with definitions of severity Secondary: SSA scale; IGA scale	Completed; no study results posted
NCT01951742	ANT-1401	Randomized, double-blind, placebo controlled	Crow's Feet (Lateral Canthal Lines)		Primary: IGA scale. Crow's Feet Wrinkle Scale Secondary: SSA score. Subjects self assessment of severity of Crow's Feet	Completed; no study results posted
NCT01809964	ANT-1401	Randomized, double-blind, placebo controlled	Lateral Canthal Lines		Primary: IGA Scale [Time Frame: Week 4] Secondary: SSA [Time Frame: Week 4]	Completed; no study results posted
NCT01293552	ANT-1207	Randomized, double-blind, placebo controlled	Acne Vulgaris		Primary: Efficacy will be assessed by lesion count. [Time Frame: Week 4] Secondary: Change from Baseline in IGA Score [Time Frame: Week 1, 2, 4, 8, and 12]. Change from Baseline in Lesion Count [Time Frame: Week 1, 2, 4, 8, 12]	Completed; no study results posted
NCT02479139	ANT-1207	Randomized, double-blind, placebo controlled	Primary Axillary Hyperhidrosis		Primary: HDSS [Time Frame: 12 Weeks]; GSP [Time Frame: 12 Weeks] Secondary: HDSS [Time Frame: Week 4, 8, and 18]; GSP [Time Frame: Week 4, 8, and 18]	Completed; no study results posted
NCT01799824	ANT-1403	Randomized, double-blind, placebo controlled	Primary Axillary Hyperhidrosis		Primary: HDSS [Time Frame: Week 8] Secondary: GSP [Time Frame: Week 8]	Completed; no study results posted

Abbreviations*, AAN Class of evidence ...; HDSS, Hyperhidrosis Disease Severity Scale; GSP, Gravimetric Sweat Production; SSA, Subject Self Assessment; IGA, Investigator Global, PSA, patient assessment of severity Assessment scale. Inflammatory lesion count (papules, pustules, and nodules) and non-inflammatory lesion count (open and closed comedones).

Table 4
Unpublished and ongoing clinical trials on botulinum toxin injections in epicardial fat pads for preventing recurrences of atrial tachyarrhythmia (source: [Clinicaltrials.gov](https://clinicaltrials.gov)).

Study	Compound	N° of patients	Trial Design	Procedure	Follow up	Outcome Measures	Results/status
NCT02982434	Pharmaceutical composition containing botulinum toxin	180	Randomized, double-blind, placebo controlled	CABG	12 months	Primary: Freedom from any atrial tachyarrhythmias; Recurrence of >30 s of any atrial tachyarrhythmia, including atrial fibrillation and atrial flutter/tachycardia, after cardiac surgery procedure with no antiarrhythmic drug. Secondary: number of deaths; time intervals from end of surgery to weaning from ventilation, extubation and discharge from ICU; incidence of congestive heart failure; incidence of sustained ventricular arrhythmias; stroke or transient ischemic attack; incidence of myocardial infarction; rehospitalization	Recruiting Estimated Study Completion Date: February 2018
NCT02498769	Botulinum Toxin Type A	130	Randomized, double-blind, placebo controlled	CABG, valve surgery or CABG + valve surgery with cardiopulmonary bypass	up to two weeks	Primary: Time to in-hospital POAF [determined by ECG or telemetry.] Secondary: Incidence of in-hospital POAF; Length of stay; Adverse events.	Recruiting Estimated Study Completion Date: July 2018
NCT02617069	Botulinum toxin injection	170	Randomized, double-blind, placebo controlled	cardiac surgery	1 month 12 months	Primary: Recurrence of >30 s of any atrial tachyarrhythmia, including AF and atrial flutter/tachycardia, after cardiac surgery procedure with no antiarrhythmic drug. Secondary: Recurrence of >30 s of any atrial tachyarrhythmia, including AF and atrial flutter/tachycardia, after cardiac surgery procedure with no antiarrhythmic drug.	Recruiting Estimated Study Completion Date: March 2017

Abbreviations: CABG, coronary artery bypass graft; POAF, postoperative atrial fibrillation; AF, atrial fibrillation.

patient undergoing coronary artery bypass graft surgery (Pokushalov et al., 2014). Sixty patients with history of paroxysmal atrial fibrillation were randomized to incoBoNT/A or placebo intra-operative treatment. Assessment was performed at 7, 14, 21, and 30 days and then at 3, 6, 9, and 12 months after injections: the incidence of AF was significantly lower in the BoNT group than in the placebo group, without serious adverse events (Pokushalov et al., 2015).

There are three registered clinical trials to assess the efficacy and safety of BoNT injection into the epicardial fat pads for preventing recurrences (in early postoperative period) of atrial tachyarrhythmia in patients undergoing cardiac surgery (NCT02982434, NCT02498769, NCT02617069). Unpublished and ongoing clinical trials on BoNT injections in epicardial fat pads for preventing recurrences of atrial tachyarrhythmia are listed in Table 4.

Radiotherapy has a crucial role in the treatment of advanced squamous cell carcinoma of the head and neck region. Unfortunately, one of the main side effect is represented by the sialadenitis. In a pilot study, 12 patients were randomized to receive onaBoNT/A or a mixture of onaBoNT/A and rimaBoNT/B or placebo (Teymoortash et al., 2016). The results do not indicate either a significant effect (as measured by scintigraphy) or a difference in salivary excretion, despite previous positive findings in a rat model (Teymoortash et al., 2007).

Keloids are firm, rubbery lesions or shiny, fibrous nodules originating from skin scars that represent esthetic, functional and psychological problems. Their management remains difficult. Among other options, BoNT/A are efficacious in the treatment and prevention of keloids (Xiao et al., 2009; Zhibo and Miaobo, 2009). The mechanism of action of BoNTs on keloids is still unknown. A reduction of tensile forces near healing wounds before collagen maturation is likely involved; in addition, BoNT is thought to influence activated fibroblast (Shaarawy et al., 2015). Six registered clinical trials aim at assessing the efficacy of BoNT in the treatment of hypertrophic scars and wounds (NCT02786550, NCT02886988, NCT02623829, NCT02168634, NCT02247193, NCT01177358, NCT01459666).

Recently, the mRNA expression profile was analyzed in keloid fibroblast after treatment with Lanzhou BoNT/A: it was observed

that the S100A4 gene is upregulated and the TGF- β 1, VEGF, MMP-1, and PDGFA genes are downregulated (Xiaoxue et al., 2014). A study evaluated the cell proliferation and cytokine secretion in cell cultures from keloids after incubation with onaBoNT/A: no significant differences in TGF- β 1, VEGF or IL-6 expressions were observed (Haubner et al., 2014).

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Transparency document

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