A 50-Week Prospective, Double–Blinded, Randomized, Cross-over design in Multicenter Study of 100 unit of Abobotulinum Toxin Type A (Dysport®) versus 33.33 unit of Neubotulinum Toxin Type A (Neuronox®) Injection For Hemifacial Spasm in Thai Patients

Study No. A-01-2020

This study was conducted in accordance with the ethical principles that had its origin in the Declaration of Helsinki and complied with the Good Clinical Practice (GCP) guidelines and the applicable regulatory requirements.

Clinical Study Protocol

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STUDY TITLE:

Phase III

A 50-Week Prospective, Double–Blinded, Randomized, Cross-over design in Multicenter Study of 100 unit of Abobotulinum Toxin Type A (Dysport®) versus 33.33 unit of Neubotulinum Toxin Type A (Neuronox®) Injection For Hemifacial Spasm in Thai Patients

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2. PROTOCOL SYNOPSIS

Name of Sponsor	Sponsor: **Medyceles Co.Ltd**
Name of Finished Product	1) Neuronox® 2) Dysport®
Name of Active Ingredient:	1) Neubotulinum Toxin Type A 2) Abobotulinum Toxin Type A
Study title	A 50-Week Prospective, Double–Blinded, Randomized, Cross-over design in Multicenter Study of 100 unit of Abobotulinum Toxin Type A (Dysport®) versus 33.33 unit of Neubotulinum Toxin Type A (Neuronox®) Injection For Hemifacial Spasm in Thai Patients
Study Phase	III
Study description	A 50-Week Prospective, Double–Blinded, Randomized, Cross-over design in Multicenter Study of, 100 unit of Abobotulinum Toxin Type A (Dysport®) and 33.33 unit of Neubotulinum Toxin Type A (Neuronox®) injection for Hemifacial Spasm in patient diagnosed with Hemifacial Spasm according to clinical diagnosis. It was designed to evaluate the efficacy, safety, tolerability, quality of life and the comparesion the improvement after treatment by of Abobotulinum Toxin Type A (Dysport®) injection versus Neubotulinum Toxin Type A (Neuronox®) Injection.
Study objectives	The primary objective of the study was to evaluate the safety and efficacy of Abobotulinum Toxin Type A (Dysport®) injection and Neubotulinum Toxin Type A (Neuronox®) Injection for Hemifacial Spasm. The secondary objective of the study was to evaluate the quality of life of Abobotulinum Toxin Type A (Dysport®) and Neubotulinum Toxin Type A (Neuronox®) Injection for Hemifacial Spasm.
Study population	120 patients diagnosed with Hemifacial Spasm were planned to be enrolled into the study. Total of 120 patients planed to be and randomized.
Study medications	Test Product: 1) Neubotulinum Toxin Type A (Neuronox®) dose was investigated: dose: 33.33 units (various units each site depend on clinical) 2) Abobotulinum Toxin Type A (Dysport®) dose was investigated: dose: 100 units (various units each site depend on clinical)

Name of Sponsor	Sponsor: **Medyceles Co.Ltd**
Name of Finished Product	1) Neuronox® 2) Dysport®
Name of Active Ingredient:	1) Neubotulinum Toxin Type A 2) Abobotulinum Toxin Type A
Criteria for evaluation	**Efficacy criteria:** **Primary efficacy variable:** Comparesion of pre- and post- treatment after 12 and 24 week scale with 33.33 unit of Neubotulinum Toxin Type A (Neuronox®) and 100 unit of Abobotulinum Toxin Type A (Dysport®); as following 1) 24 hours HFS diary record for 12 week after treatment Time to peak improvement, response duration period, Total intensity score per day, duration of facial muscle spasm (hour per day) and duration of functional impairment (hour per day) record for 12 week after each treatment will be assessed 2) Hemifacial Spasm- 30 Questionnaire (Thai version). Seven subscales (30 items). Mobility (5 items), activity of daily living (5 items) and communication (3 items) are classified as physical health domain. Emotional well-being (7 items), stigma (4 items), social support (3 items) and cognition (3 items) are classified as mental health domain 3) Abnormal involuntary movement scale (AIMS) (Thai version) Rating sacle of the severity of movements in 7 regions, each on a 5 points scale and a separate rating of the overall severity of the abnormal movements, judged on the amplitude of movements, incapacitation postures and positions, including sitting in chair, opening the mouth, tapping the thumb against each finger, holding the hand out stretched and standing and walking, are included. Dental status is also rated, as the presence or absence of problems with teeth or dentures. **Secondary efficacy variables: :** Comparesion of pre- and post- treatment after 12 and 24 week scale with 50 unit of Neubotulinum Toxin Type A (Neuronox®) and 250 unit of Abobotulinum Toxin Type A (Dysport®); as following 1) 36-item questionnaire and comprises eight domains: Physical functioning (PF), Role limitations due to physical health (RP), Role limitations due to emotional problems(RE), Vitality (VT), Mental health (MH), Social functioning (SF), Bodily pain (BP), General health (GH) 2) Center of Epidemiologic study -Depression scale (CES-D) 3) Patient health Questionnaire - 9 item (PHQ-9) 4) The investigator's /patient's global assessment of change (GAC) **Safety criteria:** The assessment of safety and tolerability were based mainly on the frequency of adverse events.

Name of Sponsor	Sponsor: **Medyceles Co.Ltd**
Name of Finished Product	1) Neuronox® 2) Dysport®
Name of Active Ingredient:	1) Neubotulinum Toxin Type A 2) Abobotulinum Toxin Type A
Statistical Methods	There were two treatment arms in crossover designed study and the interest were on the comparison of Time to peak improvement, response duration period between treatment arm, and pre- and post- treatment outcomes of (Dysport®) with (Neuronox®), two pair-wise comparisons pre- and post-treatment after 12 and 24 week scale were carried out. For each of the pair-wise comparison, 2-sided p-value was used to ensure that the overall Type I error=0.05. Beta error 80% or suitable non-parametric test. Multiple repeated analysis and general linear model will be analysed in the efficacy of treatment.Demographic and safety analyses were based on the summary of descriptive statistics. Sample size calculation was 120 patients
Efficacy Results	**Primary efficacy:** Comparesion of time to peak improvement and response duration period,and pre- and post- treatment after 12 and 24 week HFS-30 and AIMS scale with 33.33 unit of Neubotulinum Toxin Type A (Neuronox®) and 100 unit of Abobotulinum Toxin Type A (Dysport®) **Secondary Objective:** Comparesion the general quality of life (SF 36, CES-D, PHQ-9) pre- and post- 12 and 24 week treatment with 33.33 unit of Neubotulinum Toxin Type A (Neuronox®) and 100 unit of Abobotulinum Toxin Type A (Dysport®)
Size of sample	120 subjects (competitive enrolment) will be randomized and entered into the study. At least 110 subjects were included in PP analysis and all 120 subjects will be included in the ITT analysis.(drop out <10%) The sample size calculation use alpha error 0.05 Beta error 0.80
Safety Results	120 patients were included in the safety analysis. To prove the tolerability of the Abobotulinum Toxin Type A (Dysport®) and Neubotulinum Toxin Type A (Neuronox®) injection for hemifacial spasm in all the study subjects in the aspect of adverse event and serious and adverse event.

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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

GCP:	Good Clinical Practice
ICH:	International Conference on Harmonisation
IEC:	Independent Ethics Committee
BTX A:	Botulinium neurotoxin A
IHS:	International Headache Society
ITT:	Intention-To-Treat
PP:	Per-Protocol
AE	Adverse event
SAE	Serious adverse event

5. ETHICS

This study was designed, conducted and reported in accordance with the ICH-GCP guidelines (Declaration of Helsinki) and the relevant regulatory requirements.

Informed consent was obtained from all the subjects or their legal representative prior to their participation into the study.

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

All the study documents (e.g. protocol, patient informed consent, subject recruitment materials/process) and any other written information provided to subjects was submitted to the IEC for approval.

5.2 Ethical Conduct of the Study

The trial was conducted in compliance with the protocol and the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP).

5.3 Patient Information and Consent

Informed consent was obtained from the subject prior to the evaluation and screening procedure in the protocol. The subject was provided with both the informed consent form and the written information about the study. The description of the study was explained to the subject in a non-technical manner and can be easily understood.

The potential subject was given ample time to decide whether to participate in the study. Each subject was also informed that they could withdraw their consent to participate at any time at their own will.

The informed consent was then signed, dated by the subject or by the impartial witness if the subject was illiterate and by the person, normally the principal investigator and/or the co-investigators who conducted the informed consent discussion. All enrolled subjects received a copy of the signed informed consent form. Any other written information was provided prior to subject's participation in the trial.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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7. INTRODUCTION

Abobotulinum neurotoxin type A, abo-BoNT/A, (Dysport®) is the most potent biological toxin produced from *Clostridium botulinum*. In 1920, Dr Hermann Sommer of the Hooper Foundation at the University of California made the first attempt to purify the botulinum toxin. His work paved the way for further studies at Cam (Fort) Detrick on botulinum toxin type B, C, D, and E, particularly during the World War II. In 1946, Dr Carl Lammanna first crystalised the botulinum toxin type A and found it was composed of toxic units bound to non-toxic unit proteins. Dr Vernon Brooks, suggested that the botulinum toxin type A might be use to reduce the activity of hyperactive muscle in 1950s (9). In 1970-1971 Dr Alan B. Scott evolved an elegant electrophysiology EMG-guided technique to inject small doses of various agents to produce weakening of extraocular muscle for non-surgical treatment of strabismus. By 1973, he demonstrated in animal experiments that botulinum can be used for the treatment of strabismus and suggested that it might be of benefit for treating blepharospasm. In 1977, the U.S.FDA approved the botulinum toxin for human study and the result of the first clinical trial of botulinum toxin for strabismus was published in 1980. The U.S. FDA approved the botulinum toxin treatment in various movement disorders in 1990.

In 1991, the United Kingdom authorized the licence of Dysport®, and was commercially marketed by Speywood Pharmaceuticals Ltd (previously Porton Products Ltd). After it's initial success in the treatment of strabismus, Botulinum toxin was used to treat other ophthalmological conditions, such as dysthyroid ophthalmopathy (1) and nystagmus (2) blepharospasm (3), focal abnormal movement such as hemifacial spasm, spasmodic torticollis, spasticity such as dystonia and pain such as cervical and lumbar pain (4).

There has been a steady stream of ideas for other uses, such as urinary, rectal, gastroesophageal sphincter and sphincter of Oddi disturbances, cosmetic (reduction of wrinkle) and eventually tension-type headache. In the past few years, some clinical observation from Brin, MasKop reported that patients who had been injected with botulinum toxin for wrinkle had some benefit for relieving headache. Three documented studies showed the clinical use of botulinum toxin for migraine prophylaxis.(26)

Neubotulinum Toxin Type A, (Neu-BoNT/A), (Neuronox®) (Medytox Inc, Ochang-eup, Cheongwon-gu, Cheongju-si, Chungcheongbuk-do, Republic of Korea), also known as Meditoxin in Korea, is a newly manufactured BoNT-A (Neu-BoNT/A) that was developed to provide features close to onabotulinum toxin A (5). Neuronox was tested in a murine model, and its effect on muscle force generation was equivalent to Botox® (ona-BoNT/A) (6). A previous multicenter randomized controlled trial showed that Neuronox and Botox® have equivalent efficacy and safety for the treatment of spastic equinus in children with cerebral palsy (6). However, Neuronox has not yet been investigated in post-stroke upper limb spasticity and currently studied in Thai cervical dystonia patients.

7.1 Structure and pathophysiology of botulinum toxin type A

Botulinum toxin consisted of a two-chain molecule synthesized as a single polypeptide. It is cleavaged by protease into a two-chained structure consisting of a heavy

chain (molecular weight 100,000 Dalton) and a light chain molecular weight 50,000 Dalton connected by disulphide bridge (7). The heavy chain is responsible for precise targeting of the toxin to the cholinergic nerve terminals by binding irreversibly to the specific ganglioside or glycoprotein receptor site on the terminal non myelinated part of cholinergic axons. It is then actively internalized, and the light chain act by preventing calcium-dependent quantal release of acetylcholine at specific active zone on the pre-synaptic membrane. Affected neuromuscular junctions are permanently inactivated causing focal flaccid paralysis. These affected junctions can recover over weeks or months by co-lateral sprouting of motor nerve terminals and formation of neuromuscular junction.

Neubotulinum Toxin Type A (Neuronox®), features close to onabotulinum toxin A, the efficacy, duration of effect, and safety margin of each preparation was determined after delivering a single injection to the right gastrocnemius mice (0-240 U/kg body weight of neu-BoNT/A or ona-BoNT/A; 0-600 Speywood Units/kg body weight of abo-BoNT/A). Neu-BoNT/A and ona-BoNT/A may be interchangeable based on a simple dose ratio.(10)

Neu-BoNT/A (intramuscular (IM) median effective dose (ED(50)) 11.2 ± 2.7 U/kg) and ona-BoNT/A (IM ED(50) 11.9 ± 2.4 U/kg) had similar effects in terms of muscle weakness at significantly lower doses than abo-BoNT/A (IM ED(50) 41.2 ± 2.4 U/kg; $p < .001$). The safety margin (ratio between IM ED(50) and IM median lethal dose (LD(50))) of neu-BoNT/A (10.7 ± 2.6 U/kg) was also similar to that of ona-BoNT/A (10.3 ± 1.3 U/kg) but significantly higher than that of abo-BoNT/A (5.9 ± 0.4 U/kg; $p < .02$). Neu-BoNT/A and ona-BoNT/A also produced comparable patterns of response and body weight recovery by day 29.9(10)

In Thailand, Rajavithi hospital, Lampang hospital, Sapasitthiprasong hospital and Surat Thani hospital are the refereal centers for hemifacial spasm treatment. Principle investigators have experience more than 10 years. Moreover, Rajavithi center has experience in treatment of one ptients with 20 week pregnancy, spasticity, and Wilson's disease. There were no effect of Botulinum toxin A across placenta. The baby now 9 year of age with good health. There were no plubication in human and animal model identify the effect of Botulinum toxin A across placenta since Botulinum toxin A has large molecular weight. However, there were no study regarding effect of Botulinum toxin A to spermatogenesis, which needs further observation data.

7.2 Review of condition treated with botulinum toxin type A

7.2.1 Dystonia

- *blepharospasm* is the focal dystonia that affects the orbicularis oculi muscle. An intermittent or sustained closure of the eyes sometimes severe enough to cause functional blindness and Botulinum toxin type A was first used in clinical practice in 1980s in US and in 1983 in UK for this condition.
- Other dystonia such as *Neuroleptic Meige syndrome* (8).
- *Cervical dystonia* (9) is the focal dystonia affects the cervical muscle, which causes tonic or repetitive chronic posturing of the head. The preliminary studies (19) followed by controlled trials (9,20) had shown to establish botulinum toxin as the treatment of choice for cervical dystonia(21-23). After the treatment the posture was improved in 70% of the patients and 90% of the patients had a reduction in pain for the period lasting 9-15 weeks (8).

- *Oromandibular dystonia* (11, 12) affects the mastigatory muscle, lower facial and tongue muscle causes trismus, bruxism, involuntary tongue movement, and opening, closure or deviation of the jaw .In 1980s, botulinum toxin injection into the masseter, temporalis and internal pterygoid muscles reduced the oromandibular spasms and improved chewing and speech in 80% of jaw closing spasms, although 10% of patient had no benefit and showed some degree weakness of jaw closure.
- *Laryngeal dystonia* is the spasmodic dysphonia. EMG guided injection of the botulinum toxin in to the vocalis complex was used since 1989s and this treatment has revolution the treatment of adductor dystonia (13).
- *Spasmodic dystonia* (13-14), occupational cramp disorder including writer's cramp (15-19), musician cramp, golfer cramp and limb dystonia.

7.2.2 Common movement disorder

Hemifacial spasm is the benign movement disorder affected facial muscle innervated by facial nerve characterized by twitching and distort facial expression in one side of the face. This is the most common condition of the patient affecting the movement disorder clinic in Thailand as well as other Asian countries. The first double blinded cross-over design of abobotulinum toxin A (Dysport®) and Neubotulinum toxin A (Neuronox®) for hemifacial spasm was conducted in Thailand in 1985 (53). The dosage of this study is low dosage and abobotulinum toxin A (Dysport®) versus Neubotulinum toxin A (Neuronox®) convertion ration is 4.8:1 and there were no clinical significant different between quality of lif in patients with Hemifacial spasm.

7.2.3 Non-dystonic movement disorders and cervical dystonia

7.2.3.1 *Tension headache*:

Since 1997 the injections of the botulinum toxin type A to the paracranial had revolutionized the effective treatment of the tension type headaches . It was shown that the injection of botulinum toxin type A into a defined area of the pericranial muscle might be useful for the reduction of primary myalgia and secondary headache demonstrated that the injection of the botulinum toxin type A to the paracranial muscles showed an improvement in headache severity over the 4-month study period. 13 out of 22 subjects in the study showed a 15% with a 50% or >50% improvement in headache score at the 3rd month compared with only 2 out of 15 patients in the placebo group. The number of headache free days increased and was statistically significantly for subjects in the botulinum toxin type A treated group. The subjects recorded an improvement in the quality of life following botulinum toxin type A injection. It was concluded that the intramuscular injection of botulinum toxin type A was an effective treatment for chronic tension type headaches. demonstrated that the injection of the botulinum toxin in the myofascial pain syndrome and tension type headache was effective and showed a highly statistically significant difference between the two treatments in both the myofascial pain ($p<0.0001$)and tension type headache($p<0.0005$) studies. No major adverse events were reported.

7.2.3.2 Migraine :

The injection of the botulinum toxin type A in migraine subjects resulted in 51% of the subjects with complete improvement, 28 % had partial improvement and 21 % had no response.

The injection of the botulinum toxin type A (Dysport®) in tension type headache with coexisting migraine showed significant reduced area under the curve of headache (404:196 P=0.039) A multi – center, double blind, placebo controlled trial of two dosages of botulinum toxin type A in the prophylactic treatment of migraine showed reduction of the mean frequency of moderate to severe migraines from day 31^{th} to 60^{th}: The incidence of a 50 % reduction and an incidence of a decrease in 2 headaches in mild to severe migraine from day 61^{th} -90^{th}: was also shown. The other benefits shown were the reduction in the maximum severity of migraine from day 31^{th} -60^{th}: ; reduction of days with phonophobia from day 31^{th} -90^{th} and an improvement in the patient global assessment for 31^{th}-60^{th} day postinjection (21)

7.2.3.3 Cervical dystonia abnormal movement disorder

Cervical dystonia , the most commn disorder of head and neck, often suffer from twisting, distress, tremor, distortions, and severe pain in the neck muscles, possibly resulting in depression in such patients suffering from long-term illness.(27–31) A previous study in Thai patients suggests that torticollis (horizontal turning) of the neck is the most common type, followed by laterocollis (lateral flexion or tile of the neck), retrocollis (posterior extension of the neck), and anterocollis (forward flexion of the neck).(32,33) The worldwide incidence rate of CD is 0.80 per 100,000 person-years, and is predominantly observed in female patients.8 In a European study, an estimated prevalence rate of adultonset focal dystonia was 5.7 per 100,000 persons, while its prevalence rate in Thailand, primarily diagnosed as CD, was 13.6 per 100,000 persons and is predominantly found in females, especially when the patients are in their fourth to fifth decade of life.(33) Four botulinum toxins (BTXs) have been approved by the US FDA for cervical dystonia: onabotulinumtoxinA (Ona- BTX A), abobotulinumtoxinA (Abo-BTX A), incabotulinumtoxinA, and rimabotulinumtoxinB. Additionally, several guidelines recommend them as a standard treatment for CD. Since botulinum toxin A (BTX A) has the best efficacy in the treatment of CD and is able to improve the quality of life,(27,32–46) both the European Federation of Neurological Societies (EFNS) and the American Association of Neurology (AAN) have categorized BTX A in the level A recommendations and suggest it as first-line treatment.(39,47,48)

In the past, numerous oral medications, including clonazepam, anticholinergics, baclofen, levodopa, tizanidine, gabapentin, and pregabalin,were used in the treatment of CD. But now, botulinum toxintherapy is the first-line therapy and oral medications are now only infrequently used. Although there were studies of Ona-BTX A and Abo-BTX A in CD patients, which led to the medication reimbursement policy of Thailand, none of them evaluated health-related quality of life (HRQoL)after the treatment.(32,33) In addition to an efficacy of treatment, it is necessary to accurately evaluate the treatment outcomes in terms of the HRQoL for those CD patients.(36-38,45,49-52) It is known that as the physical condition improves, the HRQoL improves in CD patients, which is possibly related to the improvement of vision during reading and writing, social embarrassment, pain, depression, and anxiety. .(36-38,45,49-52) Only a few studies have evaluated the QoL of CD patientsafter treatment with Ona-BTX A and Abo-BTX. One study,in which CD patients were treated with a single injection of 30–

300 units of Neu-BTX A, illustrated a significant decrease in CD symptoms by using the Toronto Western Spasmodic Torticollis Rating scale.(33) Another study also suggested that a 3-month fixed dose of 50 units of Neu-BTX A injections was efficacious in the treatment of such patients when measuredby the Cervical Dystonia Impact Profile (CDIP-58) and CDQ-24 questionnaires.(32) Unfortunately, these short-term studies did not show improvement of general HRQoL measuredby the 36-Item Short-Form Health Survey (SF-36).(32,33) Additionally, the remaining studies did not evaluate the quality of life.(49) Consequently, long-term study assessing the TWSTRS, CDIP-59, QoL, CES-D, PHQ-9 of CD patients treated with of 50 unit of Neubotulinum Toxin Type A (Neuronox®) and 250 unit of Abobotulinum Toxin Type A (Dysport®) is currently investigated in Thai patients

7.2.3.4 Hemifacial Spasm

Previous data from a randomized, blinded study to compare the quality of life in patients with hemifacial spasm. Abo-botulinum toxin A 100 units and Neu-botulinum Toxin A 20 units were found to improve the quality of life of patients in both groups. There was no difference (HFS-30 P=0.98, SF36 p=0.34, AIMS p=084 CES-D p=0.73), However, Patient diary found that the scale indicated overall intensity (Total intensity Score) are different, Abo-botulinum toxin A 100 units can reduce the severity with an average of 8.04±0.2, which is better compared to Neu-botulinum Toxin A 20 units, which was able to reduce the severity with an average of 6.62±0.7 and the duration of facial spasm is also difference, Abo-botulinum toxin A 100 units can reduce the severity for a longer time with an average of 4.7±0.4 hours per day compared to Neu-botulinum Toxin A 20 units which can reduce it by an average of 3.64±04 hours per day. Abo-botulinum toxin A 100 unit reduced the number of hours of disability that interferes with activities of daily living by 1.73±0.2 hours per day, compared to 1.25±0.1 hours per day with 20 units of Neu-botulinum Toxin A. From the above information it is shown that Abo-botulinum Toxin A 100 units significantly reduced the severity and duration of disability that interferes with daily activities and the duration of facial pain ($P<0.001$) compared to Neu-botulinum toxin A 20 units.

Therefore a reason to perform this study, Neu-botulinum Toxin A 33.33 units compared to Abo-botulinum toxin A 100 units in patients with facial spasms, studying in a research center with neurologists with research experience Neu-botulinum Toxin A and Abo-botulinum toxin A type, double blind randomized control trial, namely Lampang Hospital, Sappasitthiprasong Hospital, Rajavithi Hospital and Surat Thani Hospital.

At present, the National Health Security Office (NHSO) has determined that no more than 400 units of Abo-botulinum toxin A can be used/year, injected at least 3 months apart (average 100 units every 3 months)but NHSO still not approved to withdraw Neu-botulinum Toxin A due to waiting for the results of research to prove the effectiveness of the drug Neu-botulinum toxin A. Thai Government reemburstmenr approved Neu-botulinum toxin A in the treatment of hemifacial spasm with c no more than 100 units per year, injected at least 3 months apart (average 25 units every 3 months), without previous studies comparing its effectiveness.

This research is the first to compare Neu-botulinum toxin A 20 units compared to Abo-botulinum Toxin A 100

The report on the safety of using neobotulinum toxin A (Neuronox) and abobotulinum toxin A (Dysport) in the treatment of facial spasms in the past composed of the study

comparing the drug neobotulinum toxin A (Neuronox) with the drug abobotulinum toxin A (Desport) in the treatment of facial spasm. C-section using low-dose neurobotulinum toxin A (Neuronox) in Thailand (Reference 53), with no reports of adverse events and Serious adverse events due to low dose use In foreign countries, there are reports of mild adverse events during 10 years of treatment with onabotulinum toxin A. (Botox) and Abobotulinum Toxin A (Dysport) are ptosis, facial weakness, double vision. which has never been reported and Serious adverse events due to low dose (Reference 56)

From the study Quality of Life in hemifacial Spasm Patient after treatment with Botulinum Toxin A; 24 - week, Double - Blind Randomized, Crossover Comparison of Dysport® and Neuronox® study by Subsai Kongsaengdao and Saksit Kritalukkul (J Med Assoc Thai 2012; 95 (Suppl. 3) : S48-S54 reference 53 found that the mean total Intensity Score of HFS at 4 weeks after treatment with Dysport® 100 units was better than Neuronox® 20 units [6.62±0.7 of Dysport vs. 8.04±02 of Neuronox. Significance level reached P<0.001] and the mean duration of facial spasms per day over 12 weeks after treatment with Dysport® 100 units was better than Neuronox® 20 units [3.64 ± 0.4 hours/day of Dysport® vs. 4.7± 0.4 hours/day of Neuronox® at the significance level P<0.001] This study shows that at a 5:1 ratio of Dysport : Neuronox, Dysport provides better treatment results in terms of severity in the first 4 weeks and duration. The duration of twitching per day over 12 weeks. This study therefore wanted to compare Dysport® 100 units with Neuronox 33.33 units (ratio 3:1) using the mean total intensity Score of HFS as the primary outcome to prove that Neuronox® 33.33 units Non-inferiority to Dysport® 100 units (non-inferiority) It is expected that Dysport® 100 units will have a mean total intensity score OF HFS of 6.62 after 4 weeks of treatment and accepts non-inferiority to Neuronox® when the mean total intensity score of HFS is 6.62±0.24 (the mean Total intensity score of HFS cannot be more than 0.24, that is, 6.86-6.38, so it is considered that the 2 drugs are not clinically different.

From the policy that focuses on providing patients with hemifacial spasm in the Thai public health system. The National Health Security Office (NHSO) requires to reembursment the use of 100 units of Dysport® for each injection every 12 weeks. In the health system by the government, which is a large expense each year. Therefore, it is necessary to conduct this research to find a way to save reasonable treatment costs. Therefore, it is necessary to study to know the efficiency and safety and the dosage of drug administration. between neurobotulinum toxin A (Neuronox), which is cheaper compared to abobotulinum toxin A (Desport) and Onabotulinum Toxin A (Botox). The results of this research will help inform the country's policy considerations. To give patients with hemiparesis disease access to treatment without wasting budget. If it is proved that 33.33 units of Neubotulinumtoxin A (Neuronox) per injection every 12 weeks is no different from Abobotulinumtoxin. A (Desport) 100 units per injection every 12 weeks, which is more expensive. Since the dose of Neuronox® 20 units per injection every 12 weeks is less effective than the dose of Dysport® 100 units per injection every 12 weeks, reference 53, making it necessary to study Neuronox® 33.33 units per injection. Each time every 12 weeks in this study.

8 STUDY OBJECTIVES

8.1 Primary Objective : To prove the non-inferiority of Total intensity score at 4 week period by comparing pre- and post- treatment after 12 and 24 week injection with 33.33 unit of Neubotulinum Toxin Type A (Neuronox®) and 100 unit of Abobotulinum Toxin Type A (Dysport®) in hemifacial spasm patients

8.2 Secondary Objective : To comparesion the quality of life (HFS 30, AIMS scale SF 36, CES-D, PHQ-9) at 4 week period by comparing pre- and post- treatment after 12 and 24 week injection with 33.33 unit of Neubotulinum Toxin Type A (Neuronox®) and 100 unit of Abobotulinum Toxin Type A (Dysport®) in hemifacial spasm patients

9. INVESTIGATIONAL PLAN

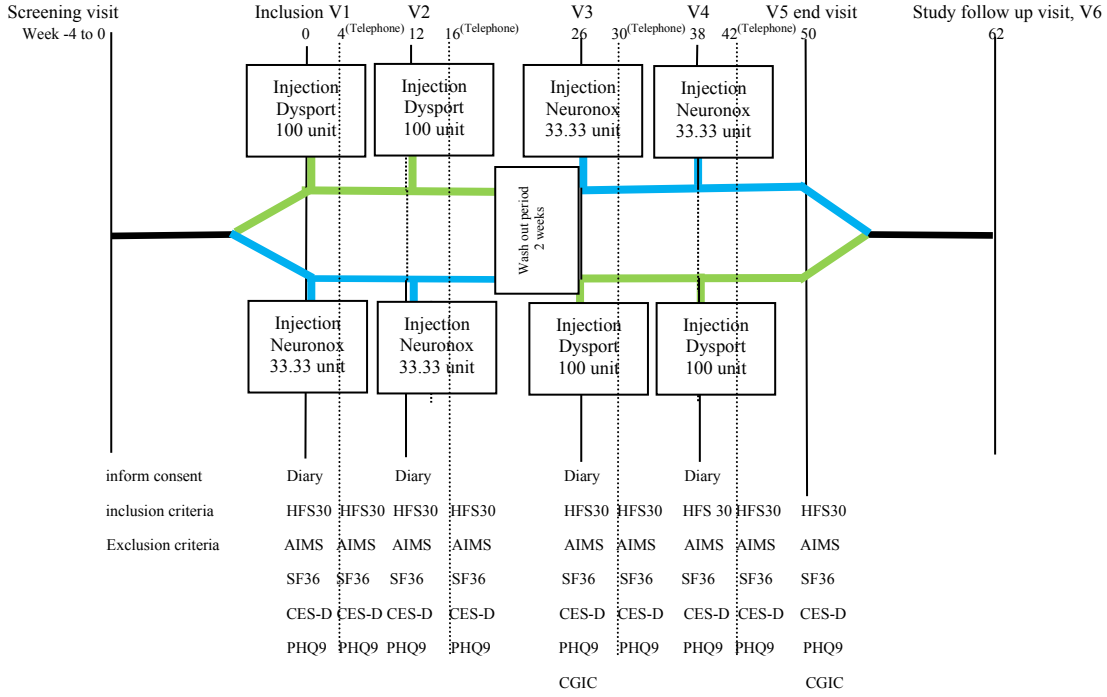
9.1 Overall Study Design and Plan There were two treatment arms in crossover designed study and the interest was on the comparison of Time to peak improvement, response duration period, and each pre- and post- treatment outcomes of (Dysport®) and (Neuronox®) , two pair-wised comparisons pre and post treatment after 12 and 24 week scale were carried out. For each of the pair-wise comparison, 2-sided p-value was used to ensure that the overall Type I error=0.05. Beta error 80% Multiple repeated analysis and general linear model will be analysed in the efficacy of treatment.Two-sided exact p-values were reported in the efficacy analyses. Demographic and safety analyses were based on the summary of descriptive statistics.

Washout period consideration

This study had a washout period of 2 weeks because there was a study on hemifacial spasm that Botulinum toxin A loses its effect before 12 weeks from a study of its action by Katalin Bihari and colleagues who found that Onabotulinumtoxin A (Botox®) has a duration of action in hemifacial spasm of 64.3 days compared to Abobotulinum toxin A (Dysport ®) has a duration of action in hemifacial spasm of 41.8 days 55 (reference Bihari K. Safety, effectiveness, and duration of effect of Botox after switching from disport for blepharospasm, cervical dystonia and hemifacial spasm. Curr Med Res Opin 2005 Mar; 21(3):433-8). Another 5 studies as follows: Lolekha (2017) found that Onabotulinumtoxin A (Botox®) had a duration of action in hemifacial spasm of 72.24 days. A, Yoshimura (1992) found that Onabotulinumtoxin A (Botox ®) has a duration of action in hemifacial spasm of 84 days. A, Rieder (2007) found that Onabotulinumtoxin A (Botox®) has a duration of action in hemifacial spasm of 71 days. A, Quagliato (2010) found that Onabotulinumtoxin A (Botox®) There is a duration of action in hemifacial spasm of 89.6 days. A and Kongsaengdao (2012) found that Neu-botulinumtoxin A (Neuronox®) / Abobotulinum Toxin A (Dysport®) had a clear measurement of the duration of action with a patient diary that recorded symptoms for everyday. The duration of action in hemifacial spasm is 84 days, which has been shown to be no different from Neubotulinum toxin This study required a washout period in this study of 14 days, which is 98 days from the second injection in V2, which is longer than the longest duration in the double blind randomized controll study. By Quagliato's (2010) which the effect in hemifacial spasm lasting for 89.6 days.

Studies which not double blinded, randomized studies with a prospective trial design and clearly measured duration of action (Duration of effect from review or estimation or inference) cannot be used as a reference for this study due to study bias.

Figure 9.1.1 Study Design



9.1.1 Pre-randomization Phase

The pre-randomization phase consisted of a screening period (0 day to 1 weeks prior to randomization).

Screening Period (-1 to 0 week):

At the screening visit and prior to performance of any study procedures, the investigators would explain the details of the study and the subject would have to sign on the written informed consent, exclusion criteria, and inclusion criteria

Each subject who was willing to enrol into the study was asked about their medical history as well as their recent and current medications being taken.

All enrolled subjects were asked to undertake an initial physical examination and had to satisfy the criteria for the inclusion /exclusion before being enrolled into the study.

All patients were asked to complete physical examination, HFS 30, AIMS, SF36, PHQ-9 and CES-D .

Laboratory blood (livers tests, haematology,) examinations, urine pregnancy test) were performed for safety reasons.

9.1.2 Double-Blind Treatment Period

9.1.2.1Inclusion visit: week 0

After the screening period, all eligible subjects were entered into the treatment period and received either intramuscular injection of 33.33 unit of Neubotulinum Toxin Type A (0.3 ml) or 100 unit of Abobotulinum Toxin Type A. (0.3 ml) The injection was only performed after the subject was confirmed to be eligible against all the inclusion and exclusion criteria.

The inclusion visit included the following examination and tests:

- physical and neurological examinations,
- vital signs,
- weight,
- urine pregnancy test result,
- CBC laboratory test result,
- HFS diary

9.1.2.2Follow up Visits V 2, V3,V4,V5,V6

Visit 2 (V2)

All subject were asked to complete physical examination, HFS 30, AIMS, SF36, PHQ-9 and CES-D and Patient Diary will be collected and dispense the new Patient diary

During of the visit, the investigator would conduct:

- physical examination and neurological examination,
- monitoring of the vital signs,
- weight measurements,
- urine pregnancy test,
- global assessment change (investigators and patient),
- adverse events,
- Co-treatment, HFS diary

after that, patient will received either intramuscular injection of 100 unit of Abobotulinum Toxin Type A. (0.3 ml) or 33.33 unit of Neubotulinum Toxin Type A (0.3 ml) as same as **Inclusion visit**

Visit 3 (V3)

All subject were asked to complete physical examination, HFS 30, AIMS, SF36, PHQ-9, CGIC and CES-D and Patient Diary will be collected and dispense the new Patient diary

During of the visit, the investigator would conduct:

- physical examination and neurological examination,
- monitoring of the vital signs,
- weight measurements,
- urine pregnancy test,
- global assessment change (investigators and patient),
- adverse events,

- Co-treatment, HFS diary

after that, patient will received either intramuscular injection of 50 unit of Neubotulinum Toxin Type A (0.3 ml) or 250 unit of Abobotulinum Toxin Type A. (0.3 ml) by crossover tretment with **Inclusion visit** and **visit 2**

Visit 4 (V4)

All subject were asked to complete physical examination, HFS 30, AIMS, SF36, PHQ-9 and CES-D and Patient Diary will be collected and dispense the new Patient diary

During of the visit, the investigator would conduct:

- physical examination and neurological examination,
- monitoring of the vital signs,
- weight measurements,
- urine pregnancy test,
- global assessment change (investigators and patient),
- adverse events,
- Co-treatment, HFS diary

after that, patient will received either intramuscular injection of 33.33 unit of Neubotulinum Toxin Type A (0.3 ml) or 100 unit of Abobotulinum Toxin Type A. (0.3 ml) as same as **visit 3**

end Visit (V5)

All subject were asked to complete physical examination, HFS 30, AIMS, SF36, CGIC PHQ-9 and CES-D and Patient Diary will be collected

During of the visit, the investigator would conduct:

- physical examination and neurological examination,
- monitoring of the vital signs,
- weight measurements,
- urine pregnancy test,
- global assessment change (investigators and patient),
- adverse events,
- Co-treatment, HFS diary

after that patient may received either intramuscular injection of 100 unit of Abobotulinum Toxin Type A. (0.3 ml) or 33.33 unit of Neubotulinum Toxin Type A (0.3 ml) by re-emburstment from national policy.

NOTE : After 4 weeks of treatment (weeks 4,16,30,42) there was a telephone call, interview, questionnaire HFS 30, AIMS, SF 36, CESD, PHQ9.

Safety follow up Visit (SFV,V6)

All subject were asked to complete physical examination, HFS 30, AIMS, SF36, and CES-D

During of the visit, the investigator would conduct:

- physical examination and neurological examination,
- monitoring of the vital signs,
- weight measurements,
- urine pregnancy test,
- global assessment change (investigators and patient),

- adverse events,
- Co-treatment, HFS diary
  after that patient may received either 100 unit of Abobotulinum Toxin Type A. (0.3 ml) or 33.33 unit of Neubotulinum Toxin Type A (33.3 ml) by re-emburstment from national policy

9.1.3 Study Population

The study population consisted of male or female subjects, ages ranged between 20-100 years old, diagnosed with hemifacial spasm. These subjects were randomized to receive 100 unit of Abobotulinum Toxin Type A (Dysport®) and 33.33 unit of Neubotulinum Toxin Type A (Neuronox®) injection in cross over designed

9.1.4 Study Duration

The study duration was conducted over 60 week (-1 to 0 week for the screening period and four of 12 week interval for the double blind cross over treatment period and 12 week follow up period.

9.2 Selection of Study Population

9.2.1Inclusion Criteria

The subjects need to satisfy the following criteria before being allowed to participate in the study:

1) Volunteers with hemifacial spasm aged 18 to 80 years who may or may not have received Botulinum toxin before.

2) Subjects were diagnosed with hemifacial spasm by a neurologist.

3) Healthy female volunteers of reproductive age must obtain informed consent from the study physician to avoid pregnancy throughout the study by using condoms or an appropriate method of birth control. too Female volunteers will be required to consent to a urine pregnancy test before entering the study and throughout the study. There will be a pregnancy test using a urine test strip every time if menstruation is over.

4) Volunteers must be evaluated for reliability in participating in the research project and volunteers or relatives can record treatment results. and side effects or drugs used in treatment They are willing to participate in the research project and understand the benefits of participating in the study.

5) The patient has had other normal physical examinations and is able to undergo a neurological examination as well as Able to participate in physical examinations to assess symptoms of hemifacial spasm and can cooperate in completing the AIMS questionnaire, HFS30, 36-item quality of life questionnaire, PHQ9, and the CES-D depression questionnaire.

9.2.2 Exclusion Criteria Criteria for exclusion from the study Patients cannot participate in the research project if they have the following conditions:

1) The volunteer is pregnant or breastfeeding, or the volunteer is a woman at risk of pregnancy who has not received adequate pregnancy protection.

2) Volunteers who have contraindications or precautions for injection. Botulinum toxin A or the need to use drugs that may cause adverse reactions from Interactions between required drugs and investigational drugs such as aminoglycoside, spectinomycin, polymyxin tetracycline, and lincomycin antibiotics and tubocurarines muscle relaxant

3) The volunteer has an allergic reaction to the drug or any substance related to the drug used for treatment.

4) The volunteer is unable or unwilling to participate and follow all details in the research project. or not cooperating in completing questionnaires in the research project

5) The subject has received any other unregistered drugs or other experimental drugs within the past 6 months. All types of botulinum toxin are allowed (patients can receive previous treatment with any type of botulinum toxin for more than 14 weeks or 98 The day before the 1st appointment)

6) Volunteers who have been previously selected for this research project.

7) Subjects with a history of botulism or co-morbidities such as neuromuscular junction disease such as myasthenia gravis. or Eaton Lumber Syndrome

8) Volunteers with other physical diseases or other neurological diseases or psychiatric disorders that may affect treatment. For example, having a history of blood clotting disorders (INR greater than 1.2), low blood platelets. Rheumatoid joint pain, heart attack, coronary artery disease Dementia Any type of psychosis or any other condition or risk factor for adverse reactions that may affect the results of the research.

9) The volunteer has a history of being addicted to or using drugs or narcotics or has a history of allergic reaction to botulinum toxin.

10) Subjects who received planned and treated surgery. throughout the research study period or patients receiving aminoglycosides or culale cannot participate in the research.

9.2.3 Removal of Patients from Therapy or Assessment

Records documenting the completion or non completion of the study by each of the subject were kept. The reason for discontinuation was recoded for any of the subjects either on the study treatment or observational aspect.

A subject might discontinue participation in the clinical study for any of the following:

Criteria for withdrawal from research Volunteers are free to withdraw from the study at any time while maintaining Continue to receive continuous care. Subjects will be withdrawn from the study if any of the following occur:
1) The volunteer experienced a serious adverse event. or interactions between drugs (Drug Interaction) such as aminoglycoside, spectinomycin, polymyxin tetracycline, and lincomycin antibiotics and tubocurarines muscle relaxant, which the researcher is of the opinion that they are not safe, such as drug allergies, facial paralysis. or weakness of the muscles used for breathing or the muscles used for swallowing. or any other muscle Subjects with severe depression based on the PHQ 9 questionnaire assessment after injection or subjects dissatisfied with non-serious adverse events. For example, unable to endure the pain of the injection or bleeding or purpura.
2) The volunteer is unwilling or unable to continue participating, or the legal guardian, guardian
Subjects were legally unwilling or unable to permit further participation in the study.
3) The investigator determined that by withdrawing the volunteer from further participation, such as the patient's facial twitching symptoms increased. or is more severe or the investigational drug has no clinical benefit after evaluation. or whether withdrawing from the research is in the best interest of the subject.
Criteria for terminating research projects The study may be terminated at any time if
1) The research project sponsor or regulatory agency has a request to stop the research. Due to safety reasons
2) Human Research Ethics Committee The Ministry of Public Health has requested to stop the research. Due to safety reasons
3) Recruitment of subjects is not as scheduled within 1 year or serious events occur more than 5 times throughout the research project.
4) The subject has any clinically significant change in medical or mental condition. (If the investigator is of the opinion that the changed condition causes the volunteer to withdraw from the study) or when there is an interaction between drugs (Drug Interaction)such as aminoglycoside, spectinomycin, polymyxin tetracycline, and lincomycin antibiotics and tubocurarines muscle relaxant
5) The subjects were required to take medications not permitted for use in the research protocol.
6) The investigator determines that the subject and/or the person assigned to care for the subject is not following study procedures or investigational medication.

9.3 Treatments

9.3.1 Treatments Administered

The study drug was administered by the investigator or by an authorised designee only in accordance with the protocol. It was forbidden to use the investigational product for purposes other than as what was defined in the Protocol.

The subject received subcutaneous injections in a syringe graduated in 0.3 ml increments and fitted with a 23 or 24 or 25 or 27 gauge needle.

The treatment regime blinding required four injection session for this study.

9.3.2 Identity of Investigational Product(s)

Dysport® was supplied as a freeze-dried powder with human serum albumin and lactose as carriers and stabilizers. Each vial contained a nominal of 500 units of the BTA. One unit was defined as the median lethal intraperitoneal dose in mice. Assuming the specific activity of purified neurotoxin to be 40 units per ng, then this represented approximatively 12,5 ng of the toxin. The freeze-dried powder had to be reconstituted with saline solution (please refer to section 5.2.3 of the protocol).

Neuronox® was supplied as a freeze-dried powder with human serum albumin and NaCl as carriers and stabilizers. Each vial contained a nominal of 100 units of the BTA. One unit was defined as the median lethal intraperitoneal dose in mice. Assuming the specific activity of purified neurotoxin to be 173.91 units per ng, then this represented approximatively 0.575 ng $\pm$ 6 pg of the toxin. The freeze-dried powder had to be reconstituted with saline solution

9.3.3 Packaging

The study treatment was presented in labelled cartons (one vial per carton). Unopened vials were maintained at a temperature between 2 and 8 C°.

9.3.4 Method of Assigning Patients to Treatment Groups

The subjects were randomly assigned to receive 100 unit of Abobotulinum Toxin Type A (Dysport®) and 33.33 unit of Neubotulinum Toxin Type A (Neuronox®) to a computer generated randomisation schedule prepared prior to the start of the study. Randomisation was used in this study to avoid bias in the assignment of the subject to the treatment groups and increased the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) were equally balanced across the treatment groups by crossover designed. The computerized generating blinding code were generated by website https://www.randomizer.org A list of treatment allocation codes for this study was prepared by the sponsor-assigned biostatistician and provided to the drug supplier, study nurse and the drug safety office in confidence.

9.3.5 Selection and Timing of Doses for Each Patient in the Study

A set of numbered randomisation envelopes were handed to the person in charge of the preparation of study treatment solution at the site (e.g.: study nurse). The allocated treatments were defined by using the randomisation envelope with the smallest number.

The study nurse would prepare the injection solution into the syringes:

- 500 unit of Abobotulinum Toxin Type A (Dysport®) was diluted with 1.5 ml of saline solution (NaCl 0,9%) [Volumes were detailed in Table 9.3.5-1]
- 100 unit of Neubotulinum Toxin Type A (Neuronox®) was diluted with 1.5 ml of saline solution (NaCl 0,9%) [Volumes were detailed in Table 9.3.5-1]
- The dilution was drawn 0.3 ml into each 29 G, 1 ml syringes for 1 syringe

Table 9.3.5-1 Preparation of study treatment

Treatment allocated by randomisation	Volume of dilution with saline solution NaCl 0.9%	Volume to draw up into each syringe
DYSPORT® 500 units	1.5 ml	1x(0.30 ml)
NEURONOX® 100 units	1.5 ml	1x(0.30 ml)

The study treatment solutions were injected within eight hours of reconstitution.

9.3.6 Blinding and Breaking of the Blind

The study site personnel (except for the study nurse preparing syringes for injection), the subjects, all the monitoring personnel, the investigators and the clinical team from the sponsor side were blinded to the assignment of the treatment to the study subjects in-order to reduce the potential bias on adverse event reporting and the outcome criteria determination.

The blinding of the study was maintained by involving a third party (the person was not involved with the patient management or assessment e.g., the study nurse) to prepare the treatment solutions. The final volume injected was the same for each treatment group (3.0 ml).

The opened randomisation envelopes were kept at a confidential place not accessible to the investigator (to maintain blinding of the investigator)

The investigator kept a set of disclosure envelopes in case of an emergency where the subject required urgent medical attention. The two other sets of disclosure envelopes were kept at the Central Department for Pharmacovigilance, Beaufour Ipsen Group.

Individual code-break envelopes were prepared to enable emergency code-break procedures of individual patients (Section 6.3.4, Protocol), without compromising the study blinding. One set was retained at the Rajavithi hospital site and one set at the investigational site.

Only in the event of an occurrence of a serious adverse event, the disclosure envelopes would be opened for a particular patient. There was no SAE reported in this study and the disclosure envelopes were kept intact.

9.3.7 Prior and Concomitant Therapy

The used of aminoglycoside antibiotics and curare were not allowed during the study. All concomitant therapies taken by the patient during the study were listed in the appendices. Concomitant therapies were summarized by the WHO Drug Reference Class.

9.3.8 Treatment Compliance

Treatment compliance was not applicable in the present study since there was only one injection session. The subjects were instructed to make follow-up visits until the end of the

study period to record on any changes in HFS 30, AIMS, SF36, and CES-D, assessments to be done using some validated questionnaires, and to monitor their safety.

9.4 Efficacy and Safety Variables

9.4.1 Efficacy and Safety Measurements Assessed and Flow Chart

The efficacy and safety measurements were assessed according to the planned visit and assessment schedule as described in Table 9.4-1. All efficacy assessments of the subjects were conducted before they received the treatment or study medication. The safety assessments consisted of the monitoring and recording of the adverse events (AEs) and serious AEs (SAEs).

Table 9.4-1 Visit and Assessment Schedule

Table of detailed procedures of the study

Evaluation schedule of the study (Initial treatment period, treatment period, and treatment follow-up)

Visit	0	1	2	3	4	5	6
Week	- 1 to 0	0	12	26	38	50	62
Process for giving consent and signing a consent form to participate	X						
Demographics data	X						
Concomitant medical history	X						
Inclusion criteria	X						
Exclusion and drop out criteria	X	X	X	X	X	X	
General and Neurological examination	X	X	X	X	X	X	X
Vital sign	X	X	X	X	X	X	X
Body weight	X	X	X	X	X	X	X
Hemifacial spasm examination		X	X	X	X	X	X
HFS 30, AIMS[&]		X	X	X	X	X	X
SF 36[&]		X	X	X	X	X	X
CES-D , PHQ 9		X	X	X	X	X	X
CBC, platelet) PT (INR) in patient with bleeding tendency	X	X	X	X	X	X	
Urine pregnancy test		X	X*	X*	X*	X*	X*
HFS diary and adverse event		X	X	X	X	X	X
CGIC- physician				X		X	
CGIC- patient				X		X	

&After 4 weeks of treatment (weeks 4,16,30,42) there was a telephone call, interview, questionnaire HFS 30, AIMS, SF 36, CESD, PHQ9.

*in case of abnormal menstruation

9.5 Efficacy Variable(s)

9.5.1 Primary efficacy variable

Primary outcomes is used the conclusiom of this study, to proved. Comparesion of time to peak improvement, response duration period, and pre- and post- treatment after 12 and 24 week HFS 30 and AIMS scale in 33.33 unit of Neubotulinum Toxin Type A and 100 unit of Abobotulinum Toxin Type A.

9.5.2 Secondary efficacy variable(s)

General Quality of life (SF-36) and depression scale (CED-20) Comparesion of pre and post treatment after 12 and 24 week scale with 33.33 unit of Neubotulinum Toxin Type A and 100 unit of Abobotulinum Toxin Type A the investigator's global assessment of change at each visit compared to the baseline (Scores from - 3 very much improved to + 3 very much deteriorated), the patient's global assessment compared to the baseline (Scores from - 3 very much improved to + 3 very much deteriorated), the rate of responders (a patient was considered a responder if there was an improvement in the two global assessments of change), the SF-36 scores**.**

9.5.1.2 Safety and tolerability evaluation

Safety was assessed by the recording of adverse events.

9.6 Data Administration, Management and Quality Control

9.6.1 Method of Data Collection and Recording

The investigator or the designated study staff at the investigational site was responsible for all the data and results from the clinical and laboratory examinations and were entered on a regular basis onto the case record forms (CRFs) from the Rajavithi hospital site. The investigator was responsible for designating an appropriate qualified staff to complete the CRFs and completing the signature log. All CRF entries were made legibly in indelible ink. Completed CRFs were signed on-site and made available for the CRAs for review and verification during the monitoring visits. Queries were made on any discrepancies and unusual data in the CRFs and to be resolved with the investigator by the CRA.

Any corrections made in the entries of the CRF and in the source documents must not obscured the original entry. Corrections made must be initialled and dated by the relevant person and an explanation for the correction detailed.

9.6.2 Source Data Verification

Data captured were verified against the source document by the Rajavithi hospital site in accordance with the GCP guidelines. The medical records from the subjects were viewed by the Rajavithi neurological research-authorised personnel and by the local and possibly foreign regulatory authorities. The permission to view the medical records would have been granted by the subject in the informed consent.

9.6.3 Submission of Data to Rajavithi Hospital

CRFs were completed in a timely manner and were regularly reviewed by the study monitor. CRFs were made available for collection within a month of each completed visit.

Whenever a subject's name was revealed on a document that had to be submitted to the Rajavithi hospital site (e.g. informed consent, laboratory print-outs) the name was deleted

out permanently by the site personnel, leaving the initials visible, and annotated with the subject's number as an identification.

9.6.4 Data Quality Control

Once the CRFs were transferred to Rajavithi neurological research, these CRFs were reviewed again (secondary monitoring) for completeness, consistency, legibility and protocol compliance. Reasons were given on the relevant CRF or compliance page for any missing data and other protocol deviations. Data management queries and other items not adequately explained were returned to the investigator by the CRA for clarification/correction. The investigator ensured that data queries were dealt with promptly. Copies of all data changes and clarifications were retained by the investigator and filed with the CRFs.

9.6.5 Record Keeping at the Investigational Site

The investigator were responsible for the arrangement to retain the CRFs and GCP-defined essential documentation, including correspondence, source documents and the confidential listing of patient names and numbers, for not less than two years after the last approval of a marketing authorisation in an ICH region, or for longer if required by local regulations. The archiving arrangements were addressed by the monitor when closing-out the site.

9.7 Statistical Methods Planned in the Protocol and Determination of the Sample Size

The statistical methods and analyses of the data were conducted by Associate Professor Dusit Sujirarat , Mahidol University.

It was planned that the data from all the centres that participated in this protocol were combined so that an adequate number of patients would be made available for the analysis.

9.7.1 Statistical and Analytical Plans

9.7.1.1 Patient Classification and Definitions

Certain terms were used for the subject classification in-order to classify a subject's status during the time of completing or leaving the study:

- **Recruited subject:** Subject fully informed about the study that gave written informed consent to participate (before any trial related procedure) and complied with all eligibility criteria.
- **Completed subject:** Recruited subject who has completed all specified phases of the study according to the protocol. This group may include protocol violators, which would affect the analysis status.
- **Drop-out:** Recruited subject who did not complete the study according to the protocol. The "drop-out" patient was notified to the sponsor/monitor as soon as possible.

- **Drop-out prior to drug exposure:** Recruited subject who did not proceed to the treatment phase of the study. Although not exposed to study medication, they had been exposed to the procedures of the study and study records up to the time of drop-out and the final evaluation was completed including the reason for withdrawal.

9.7.1.2 Evaluable Data

Data obtained from all recruited subjects known to have received any treatment and who provided any follow up data for one or more key efficacy variables were analysed in accordance with intent-to-treat methods.

9.7.1.3 Type Analyses

The objective of the present study was to determine the efficacy (time to peak improvement, response duration period) and tolerability of 100 unit Dysport® and 33.33 unit Neuronox® compare to base line HFS 30, AIMS, SF36, PHQ-9 and CES-D

The statistical analyses carried out were:

- Time to peak improvement, response duration period between group treatment 100 unit Dysport® and 33.33 unit Neuronox® at week 12, 24
- Between baseline (pre) and post 12 and 24 week treatment of 100 unit Dysport® and 33.33 unit Neuronox®

The data obtained were summarized with respect to the demographic and the baseline characteristics, efficacy observations and measurements, the safety observations and measurements. For all continuous variables, summary statistics (mean, standard deviation, and median, minimum, maximum) were provided for each of the three groups.

For all categorical variables, frequency distribution was provided for each of the two groups. The significance level of statistical test was 0.05. There were two treatment arms in crossover designed study and the interest was only on the comparison of each outcome of (Dysport®) with (Neuronox®) Multiple repeated analysis and general linear model will be analysed in the efficacy of treatment.

Populations

All subjects who received at least one dose of study medication and who did have subsequent safety evaluation/s were included in the safety database (safety population).

For efficacy, an Intention-to-Treat (ITT) population and a Per Protocol (PP) population were defined.

The intent-to-treat population analysis included all the subjects who were:

1) Assessed at the inclusion visit,
2) Received the dose of trial medication,
3) Assessed once after the inclusion visit,

A "Per-Protocol" population, subset of the previous one, was defined to include all subjects who had no major protocol deviation.

The definition of the "Per-Protocol" population was followed before breaking of the blind.

Background and Demographic Characteristics

Background and relevant baseline information was presented and summarized for both the Safety and the ITT populations with appropriate descriptive statistics.

Efficacy Evaluation

The efficacy parameters were presented descriptively for the ITT and the PP population. The primary analysis was performed on the ITT population. The analysis was carried out only on observed cases.

Primary Efficacy Variables

Primary efficacy is comparesion of Time to peak improvement, response duration period between group treatment 100 unit Dysport® and 33.33 unit Neuronox® at week 12, 24 and alsp pre- and post-treatment after 12 and 24 week HFS 30 and AIMS scale with 33.33 unit of Neubotulinum Toxin Type A and 100 unit of Abobotulinum Toxin Type A.

Secondary outcomes is comparesion of General Quality of life (SF-36) and PHQ 9 ,depression scale (CED-20) Comparesion of pre and post treatment after 12 and 24 week scale with 33.33 unit of Neubotulinum Toxin Type A and 100 unit of Abobotulinum Toxin Type A

Two pair-wise comparisons pre- and post- treatment after 12 and 24 week scale were carried out. For each of the pair-wise comparison, 2-sided p-value was used to ensure that the overall Type I error=0.05. Beta error 80% or suitable non parametric test.

Multiple repeated analysis and general linear model will be analysed in the efficacy of treatment. Demographic and safety analyses were based on the summary of descriptive statistics.

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Secondary Efficacy Variables

Secondary outcomes is comparesion of General Quality of life (SF-36) and depression scale (CES-D) Comparesion of pre and post treatment after 12 and 24 week scale with 33.33 unit of Neubotulinum Toxin Type A and 100 unit of Abobotulinum Toxin Type A. Questionnaire SF-36: the values of the eight dimensions of the SF36 were calculated and presented descriptively. For each dimension, a repeated measures analysis was performed.

Safety and Tolerability Evaluation

The assessment of safety and tolerability was based mainly on the frequency of the occurrence of adverse events. Other safety data (e.g. vital sign) was considered as appropriate.

Adverse events were summarized by presenting the number and percentage of subjects with any adverse events in individual and in each body system. Any other information collected (e.g. severity or relatedness to study medication) was listed as appropriate. Data from other tests (e.g. vital signs) were listed, notable values were flagged, and any other information collected was listed as appropriate. Any statistical tests performed to explore the data were used only to highlight any interesting comparisons that may warrant further consideration.

Study Medication

Listings with drug administration record were presented for each patient. Compliance was not assessed as no drug accountability was recorded.

9.7.2 Determination of Sample Size (non-inferiority design)

The present study was designed as an exploratory study. The sample size was following:

By reference 53, Mean total intensity Score of HFS was used as Primary outcome to prove noninferiority or superiority between Neuronox® 33.33 unit and Dysport® 100unit. The estimated mean total intensity score OF HFS in Dysport® 100 unit group after 4 week treatment was 6.62 and accepted noninferiority margin of mean total intensity score of HFS in Neuronox® group with 6.62±0.24 (error = 0.24 by mean total intensity score 6.86-6.38)

1) Mean Group Dysport® 100ū has Total intensity score of HFS μ_1 ($\mathbf{m}_1$)= 6.62)
2) Mean Group Neuronox® 33.33ū hasTotal intensity score of HFS μ_2 ($\mathbf{m}_1$) = 6.62)

3) Standard deviation by sd of Dysport® ق $_1$= 0.7 and Neuronox ®ق $_2$= 0.7

4) Non inferiority or Superiority margin $\delta = 0.36$

5) Sample size Ration K= $\eta_1/\ \eta_2$= 1:1 (crossover design study)

6)$\alpha = 0.05$ $Z_{1-\alpha} = Z_{0.95} = 1.96$

7)$\beta = 0.80$ $Z_{1-\beta} = Z_{0.80} = 1.28$

Compare2means 2 sample Non inferiority or Superiority statistic by formula as followings:

Sample size $(n) = \frac{(z_{1-\alpha}+z_{1-\beta})^2[\vartheta_1+\vartheta_2]}{[d-(m_1-m_2)]^2}$

Sample size $(n) = \frac{(1.96+1.28)^2[0.7+0.7]}{[0.36-(6.62-6.62)]^2}$

$= \frac{14.69664}{0.1296}$

$= 113.34$

Total estimated sample size per group=114 subjects
Estimated Drop out 5% (n =6) subjects
Recruitment sample size = 120 subjects

9.8 Changes in the Conduct of the Study or Planned Analyses

The protocol changes will be documented in Appendix in the study Protocol.

REFERENCE LIST

1. Evers S., Vollmer-Haase J., Schwaag S., et al. Botulinum toxin A in the prophylactic treatment of migraine- a randomized, double-blind, placebo-controlled study. Cephalalgia, 2004, 24,838-43.
2. Dodick DW., Rojer LR. Hentz JG, et al. The effect of botulinum toxin type A headache related disability in migraine sufferers: a double blind, randomized, placebo controlled study. Cephalalgia 2005;25:992.[Abstract]
3. Silberstein SD., Methew N., Saper J., et al. Botulinum toxin type A as migraine preventive treatment. Headache. 2000; 40:445-50.
4. Turton K., Chaddock JA., Acharya KR. Botulinum and tetanus neurotoxins: structure, function and therapeutic utility. Trends Biochem. Sci. 2002; 27: 552-8.
5. Stone AV, Ma J, Whitlock PW, Koman LA, Smith TL, Smith BP, et al. Effects of Botox and Neuronox on muscle force generation in mice. J Orthop Res. 2007;25(12):1658–64. doi: 10.1002/jor.20450 .[PubMed]
6. Kim K, Shin HI, Kwon BS, Kim SJ, Jung IY, Bang MS. Neuronox versus BOTOX for spastic equinus gait in children with cerebral palsy: a randomized, double-blinded, controlled multicentre clinical trial. Dev Med Child Neurol. 2011;53(3):239–44. Epub 2010/11/23. doi: 10.1111/j.1469-8749.2010.03830.x .[PubMed]
7. Brin MF., Botulinum toxin: chemistry, pharmacology, toxicity, and immunology. Muscle Nerve. 1997;20:S146-S168.
8. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders. Cephalalgia. 2004; 24: Suppl 1:24-43.
9. Tepper SJ, Bigal ME, Sheftell FD, et. al. Botulinum neurotoxin type A in the preventive treatment of refractory headache: a review of 100 consecutive cases. Headache. 2004 Sept; 44(8): 794-800.
10. Kim SB[1], Ban B, Jung KS, Yang GH. A pharmacodynamic comparison study of different botulinum toxin type A preparationsPLoS One. 2015; 10(6): e0128633.

11. Stewart WF, Lipton RB, Kolodner KB, et.al. Validity of the Migraine Disability Assessment (MIDAS) score in comparison to a diary-based measure in a population sample of migraine sufferers. Pain. 2000 Oct; 88(1):41-52.
12. Cui M., Akoi KR., Botulinum toxin type A reduces inflammatory pain in rat formalin model. Cephalagia. 2000; 20:414.
13. Gobel F., Heinze A., Kuhn KH., et. al. Botulinum toxin type A in the treatment of headache syndromes and pericranial pain syndrome. Pain. 2001; 91:195-9.
14. Borodic GE., Acquardro M., Johnson EA., Botulinum toxin therapy for pain and inflammatory disorders: mechanisms and therapeutic effects. Expert Opin Investig Drugs. 2001; 10:1531-44.
15. Arezzo, JC 2002. Possible mechanism for the effects of Botulinum toxin on pain. Clin. J Pain 2002; 18:S125-S132.
16. Kramer HH. Angerer C. Erbguth F. et al. Botulinum toxin A reduce neurogenic flare but has almost no effect on pain and hyperalgesia in human skin. J Neurol. 2003: 188-93.
17. Blersch W., Schutle M JW., Przywara S. et al. Botulinum toxin A and the cutaneous nociception in humans: a prospective, double blind, placebo controlled, randomized study. J Neurol Sci 2002; 205:59-63.
18. Caputi CA. Effectiveness of BoNT-A in the treatment of migraine and its ability to repress CGRP release. Headache. 2004 Sep; 44(8): 837-8.
19. Smuts JA, Schultz D, Barnard A. Mechanism of action of botulinum toxin type A in migraine prevention: a pilot study. Headache. 2004 Sep; 44(8): 801-5.
20. Durham PL, Cady R. Regulation of calcitonin gene-related peptide secretion from trigeminal nerve cells by botulinum toxin type A : implications from migraine therapy. Headache. 2004 Jan; 44(1): 35-42; discussion 42-3.
21. Silberstein SD. Review of botulinum toxin type A and its clinical applications in migraine headache. Expert Opin Pharmacother. 2001 Oct; 2(10):1649-54.
22. Aoki KR. Evidence for antinociceptive activity of botulinum toxin type A in pain management. Headache. 2003 Jul-Aug; 43 Supp 11: S9-15.
23. Blumenfeld AM, Dodick DW, Silberstein SD. Botulinum neurotoxin for the treatment of migraine and other primary headache disorders. Dermatol Clin. 2004 Apr; 22(2):167-75.
24. Gobel H. Botulinum toxin in migraine prophylaxis. Neurol. 2004 Feb; 251 Suppl 1:8-11.
25. Silberstein S, Mathew N, Saper J, Jenkins S. Botulinum toxin type A as a migraine preventive treatment. For the BOTOX Migraine Clinical Research Group. Headache. 2000 Jun;40(6):445-50.
26. Chankrachang S, Arayawichanont A, Poungvarin N, Nidhinandana S, Boonkongchuen P, Towanabut S, Sithinamsuwan P, Kongsaengdao S. Prophylactic botulinum type A toxin complex (Dysport®) for migraine without aura. Headache. 2011 Jan;51(1):52-63
27. Jankovic J. Treatment of dystonia. *Lancet Neurol*. 2006;5(10):864–872.
28. Comella CL, Thompson PD. Treatment of cervical dystonia with botulinum toxins. *Eur J Neurol*. 2006;13(Suppl 1):16–20.
29. Chan J, Brin MF, Fahn S. Idiopathic cervical dystonia: clinical characteristics. *Mov Disord*. 1991;6(2):119–126.

30. de Carvalho Aguiar PM, Ozelius LJ. Classification and genetics of dystonia. *Lancet Neurol*. 2002;1(5):316–325.
31. Bressman SB, Greene PE. Dystonia. *Curr Treat Options Neurol*. 2000; 2(3):275–285.
32. Kongsaengdao S, Maneeton B, Maneeton N. Quality of life in cervical dystonia after treatment with botulinum toxin A: a 24-week prospective study. *Neuropsychiat Dis Treat*. 2017;13:127–132.
33. Jagota P, Kaewwilai L, Boonrod N, et al. Impact of neu-botulinumtoxinA on the severity and quality of life of cervical dystonia patients. *Tremor Other Hyperkinet Move*. 2016;6:407.
34. Epidemiological Study of Dystonia in Europe Collaborative Group.A prevalence study of primary dystonia in eight European countries. *J Neurol*. 2000;247(10):787–792.
35. Slawek J, Friedman A, Potulska A, et al. Factors affecting the healthrelated quality of life of patients with cervical dystonia and the impact of botulinum toxin type A injections. *Funct Neurol*. 2007;22(2):95–100.
36. Costa J, Espirito-Santo C, Borges A, Ferreira JJ, Coelho M, Sampaio C. Botulinum toxin type A versus anticholinergics for cervical dystonia. *Cochrane Database Syst Rev*. 2005;(1):CD004312.
37. Walker FO. Botulinum toxin therapy for cervical dystonia. *Phys MedRehabili Clin N Am*. 2003;14(4):749–766,
38. Simpson DM, Blitzer A, Brashear A, et al. Assessment: botulinumneurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2008; 70(19):1699–1706.
39. Ferreira JJ, Costa J, Coelho M, Sampaio C. The management of cervicaldystonia. *Expert Opin Pharmacother*. 2007;8(2):129–140.
40. Brashear A. The botulinum toxins in the treatment of cervical dystonia. *Sem Neurol*. 2001;21(1):85–90.
41. Cano SJ, Hobart JC, Edwards M, et al. CDIP-58 can measure the impact of botulinum toxin treatment in cervical dystonia. *Neurology*. 2006;67(12):2230–2232.
42. Brans JW, Lindeboom R, Aramideh M, Speelman JD. Long-term effect of botulinum toxin on impairment and functional health in cervical dystonia. *Neurology*. 1998;50(5):1461–1463.
43. Pekmezovic T, Svetel M, Ivanovic N, et al. Quality of life in patients with focal dystonia. *Clin Neurol Neurosurg*. 2009;111(2):161–16
44. Hakkinen A, Ylinen J, Rinta-Keturi M, Talvitie U, Kautiainen H, Rissanen A. Decreased neck muscle strength is highly associated with pain in cervical dystonia patients treated with botulinum toxin injections. *Arch Phy Med Rehab*. 2004;85(10):1684–1688.
45. Hilker R, Schischniaschvili M, Ghaemi M, Jacobs A, Rudolf J. Health related quality of life is improved by botulinum neurotoxin type A in long term treated patients with focal dystonia. *J Neurol Neurosurg Psychiatry*. 2001;71(2):193–199.
46. Wenzel T, Schnider P, Wimmer A, Steinhoff N, Moraru E, Auff E. Psychiatric comorbidity in patients with spasmodic torticollis. *J Psychosom Res*. 1998;44(6):687–690.

47 Albanese A, Asmus F, Bhatia KP, et al. EFNS guidelines on diagnosis and treatment of primary dystonias. *Eur J Neurol*. 2011;18(1):5–18.

48. Albanese A, Barnes MP, Bhatia KP, et al. A systematic review on the diagnosis and treatment of primary (idiopathic) dystonia and dystonia plus syndromes: report of an EFNS/MDS-ES Task Force. *Eur J Neurol*. 2006;13(5):433–444.

49. Poungvarin N, Viriyavejakul A. Botulinum A toxin treatment in spasmodic torticollis: report of 56 patients. *J Med Assoc Thai*. 1994;77(9):464–470.

50. Hefter H, Benecke R, Erbguth F, Jost W, Reichel G, Wissel J. An openlabel cohort study of the improvement of quality of life and pain in de novo cervical dystonia patients after injections with 500 U botulinum toxin A (Dysport). *BMJ Open*. 2013;3(4):e001853.

51. Skogseid IM, Malt UF, Roislien J, Kerty E. Determinants and status of quality of life after long-term botulinum toxin therapy for cervical dystonia. *Eur J Nurol*. 2007;14(10):1129–1137.

52. Mordin M, Masaquel C, Abbott C, Copley-Merriman C. Factors affecting the health-related quality of life of patients with cervical dystonia and impact of treatment with abobotulinumtoxinA (Dysport): results from a randomised, double-blind, placebo-controlled study. *BMJ Open*. 2014;4(10):e005150.

53. Kongsengdao S , Kritalukkul S Quality of life in hemifacial spasm patient after treatment with botulinum toxin A; a 24-week, double-blind, randomized, cross-over comparison of Dysport and Neuronox study. J Med Ass Thai 01 Mar 2012, 95 Suppl 3:S48-54

54. Kongsaengdao S, Maneeton B, Maneeton N. Long-term Quality of life in cervical dystonia after treatment with botulinum toxin A: a 2-year prospective study. Neuropsychiat Dis Treat. 2018;1119-1124.

55. Kongsaengdao S A 48-Week Prospective, Double-Blinded, Randomized, Cross-over Design in Multicenter Study of 250 Unit of Dysport Versus 50 Unit of Neuronox Injection For Cervical Dystonia in Thai Patients. Clinical trial register NCT 03805152

56. Somsak Tiamkao, Supinya Tuntapakul, Kittisak Sawanyawisuth, and Suthipun Jitpimolmard.

Clinical efficacy of Neuronox® botulinum toxin treatment in hemifacial spasm patients

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