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Effect of early use of AbobotulinumtoxinA after stroke on spasticity progression: Protocol for a randomised controlled pilot study in adult subjects with moderate to severe upper limb spasticity (ONTIME pilot)

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ABSTRACT

Introduction: Approximately 15 million people suffer a stroke annually, up to 40% of which may develop spasticity, which can result in impaired limb function, pain and associated involuntary movements affecting motor control.

Robust clinical data on spasticity progression, associated symptoms development and functional impairment is scarce. Additionally, maximal duration of muscle tone reduction following botulinum toxin type A (BoNT-A) injections remains undetermined. The ONTIME pilot study aims to explore these issues and evaluate whether abobotulinumtoxinA 500 U (Dysport®; Ipsen) administered intramuscularly within 12 weeks following stroke delays the appearance or progression of symptomatic (disabling) upper limb spasticity (ULS).

Methods: ONTIME is a 28-week, phase 4, randomised, double-blind, placebo-controlled, exploratory pilot study initiated at four centres across Malaysia, the Philippines, Singapore and Thailand. Subjects (n = 42) with moderate to severe ULS (modified Ashworth scale [MAS] score ≥2) in elbow flexors or pronators, wrist flexors, or finger flexors will be recruited. Subjects will be randomised 2:1 to abobotulinumtoxinA 500 U or placebo (single dose 2–12 weeks after first-ever stroke).

Primary efficacy will be measured by time between initial injection and visit at which reinjection criteria (MAS score ≥2 in the primary targeted muscle group and appearance or reappearance of symptomatic ULS) are met. Follow-up visits will be 4-weekly to a maximum of 28 weeks.

Discussion: This pilot study will facilitate the design and sample size calculation of further confirmatory studies, and is expected to provide insights into the optimal management of post-stroke patients, including timing of BoNT-A therapy and follow-up duration.

1. Introduction

An estimated 15 million people suffer a stroke annually [1]; of whom, up to 40% develop post-stroke spasticity, a state of velocity-dependent increase in tonic stretch reflexes ('muscle tone') with exaggerated tendon jerks [2] most commonly affecting upper limbs [3–7]. Post-stroke spasticity impedes active and passive functioning of affected limb(s), impairs activities of daily living and requires long-term treatment; associated healthcare costs are up to four-fold greater than for stroke survivors without spasticity [7].

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; eCRF, electronic case report form; FU, follow-up; MAS, modified Ashworth scale; IM, intramuscularly; MRS, modified Rankin scale; NPRS, numeric pain rating scale; RC, reinjection criteria; ULS, upper limb spasticity.

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Furthermore, spasticity may involve pain and involuntary movements, interfering with dressing, gait, balance and walking speed, and can disrupt rehabilitation [8]. Without functional improvement, secondary musculoskeletal complications such as contractures and deformity may develop [9].

Data on the proportion of patients with post-stroke spasticity developing disability are scarce. One survey (N = 140) reported a prevalence of 17% spasticity and 4% disabling spasticity with a year [4]. Upper limb involvement and age <65 years were associated with disabling spasticity in this study [4]. In other studies, over a third of individuals developed spasticity within a year, including 20% with severe spasticity [10,11], suggesting higher rates of disabling spasticity than those reported by Lundström et al. [4].

Studies evaluating the timeframe for developing spasticity symptoms post-stroke are also few, with small cohorts (around 100 patients), but suggest the prevalence and severity of spasticity increases within a year post-stroke [5,6,10–13]. Certain studies indicate that spasticity symptoms and muscle tone changes are apparent in up to 25% of stroke victims within 2 weeks [3,5,14]. One study reported increased muscle tone as an early risk factor for developing severe disabling spasticity, particularly if it affected more than two joints, or was associated with a modified Ashworth scale (MAS) score ≥2 in one affected joint within 6 weeks post-stroke [14]. Indeed, spasticity may persist [15], and the severity of upper limb spasticity (ULS) may increase over time, most commonly affecting anti-gravity muscles, during the first 2 weeks and at 3 months post-stroke [5].

AbobotulinumtoxinA is an effective focal intervention for reducing ULS [16] and coupled with neurorehabilitation is recommended in standard clinical practice [17,18]. Treatment with botulinum toxin A (BoNT-A) is generally delayed in post-stroke spasticity until patients show clinical signs of increased muscle tone, usually about 3 months following stroke [19], despite evidence that symptoms begin much earlier.

Recent studies aimed to evaluate whether earlier post-stroke treatment with BoNT-A may prevent disabling spasticity development [15,19,20] and demonstrate that BoNT-A administered within 3 months provides sustained improvement in muscle tone. However, there is a paucity of robust clinical data on spasticity progression timeframes, associated symptom development, functional impairment, and maximal duration of muscle tone reduction with BoNT-A.

The ONTIME pilot study explores these foregoing issues to establish whether treatment with abobotulinumtoxinA (Dysport®) within 2–12 weeks post-stroke might delay symptomatic or disabling spasticity development, and to assess the duration of this effect. Importantly, this study incorporates composite measure of active and passive functionality, involuntary movements and pain.

2. Methods and analysis

2.1. Objectives

2.1.1. Primary objective

To evaluate whether abobotulinumtoxinA 500 U administered intramuscularly within 12 weeks following stroke will delay the appearance or the progression of symptomatic spasticity of the upper limbs, as defined by the requirement for reinjection of abobotulinumtoxinA determined by a MAS score of 2 or more and concomitant measures of related pain, passive function, active function and involuntary movements.

2.1.2. Secondary objectives

1. To evaluate the efficacy of abobotulinumtoxinA on muscle tone (MAS) in the primary targeted muscle group selected from the following muscle groups: elbow flexors or pronators, wrist flexors, or finger flexors.
2. To assess the efficacy of abobotulinumtoxinA based on the time interval between abobotulinumtoxinA injection and requirement for reinjection as determined by protocol-defined criteria and stratified by symptomatic and asymptomatic spasticity.
3. To explore the efficacy of abobotulinumtoxinA early intervention after stroke on upper limb motor impairment.
4. To assess the use of non-drug therapy sessions received for ULS in combination with study treatment injections.
5. To document subjects' demographic and stroke-related clinical characteristics and disability at the first visit after stroke.
6. To assess the subject's overall improvement since the first visit based on an investigator global assessment of change.

2.1.3. Safety objectives

1. To monitor the occurrence of treatment-emergent adverse events and determine any suspected association with study medication.
2. To assess clinically significant changes in subject's physical condition and vital signs, including blood pressure, heart rate, body temperature and weight.

2.2. Study design and setting

The ONTIME pilot study is a 28-week, phase IV, randomised, double-blind, placebo-controlled, exploratory trial. Full details of the study design and conduct are detailed in the study protocol [Ipsen Pharma. Data on file. Asian Multicenter, Double Blind, Randomised, Placebo Controlled Pilot Study, to Assess the Impact of Dysport® Intramuscular Injections When Administered Within the First 12 Weeks After Stroke on the Time to Spasticity Progression in Adult Subjects with Upper Limb (UL) Spasticity. Study Protocol. Study Number Y-79-52120-197 (ONTIME PILOT). Final Version 1.0 ONTIME PILOT 06 March 2014]. The proof of concept for the present study was primarily based on observations derived from the ABCDE-S trial, regarding the placebo and injected cohorts [15]. The trial has been initiated in four study locations: one center each in Malaysia, the Philippines, Singapore and Thailand. At present, recruitment has been completed and data collection is ongoing. An overview of the study design is shown in Fig. 1.

2.3. Recruitment

Male and female adult Asian subjects who meet the following inclusion criteria will be eligible to be enrolled onto the study; recruitment will stop once 42 evaluable subjects have been randomised. It is planned that 40–60% of subjects in each treatment group will present with symptomatic spasticity and 40–60% with asymptomatic spasticity.

2.4. Inclusion criteria

- 18 (or age of consent according to national law) to 80 years of age.
- Presenting 2–12 weeks after first ever stroke according to World Health Organisation criteria. Ischemic/hemorrhagic stroke as confirmed by computerised tomography (CT) or magnetic resonance imaging (MRI). Previous transient ischemic attack or

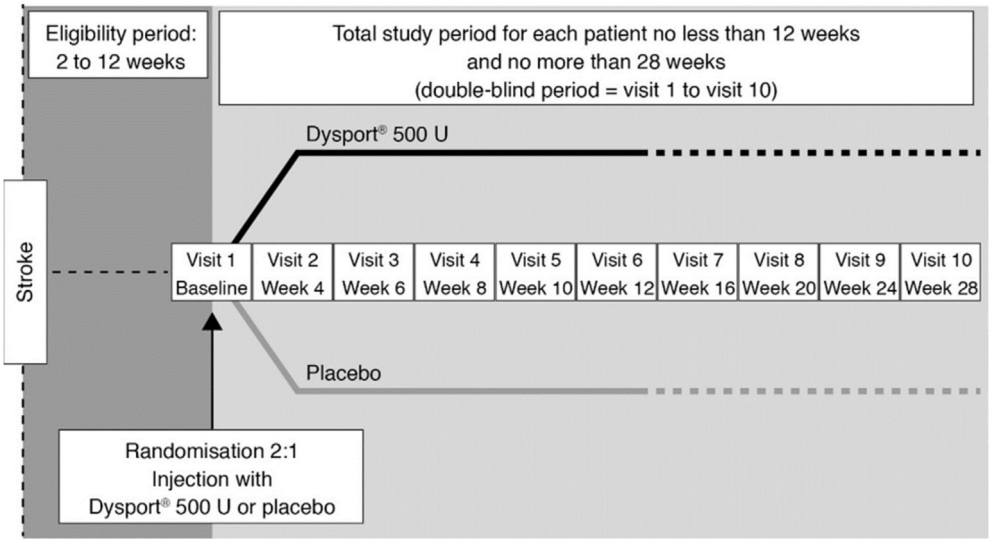

Fig. 1. Overview of study design.

clinically silent infarct detected by CT/MRI are not to be considered as previous stroke.
- Presence of spasticity, either symptomatic or asymptomatic, in the relevant upper limb. Symptomatic spasticity is defined as having at least one of the following items: impaired passive or active function score ≥1 on a 4-point Likert scale; presence of involuntary movements score ≥1 on a 4-point Likert scale; pain score ≥4 on a numeric pain rating scale (NPRS) (Table 1) [21] on top of increased muscle tone (MAS score ≥2). Asymptomatic spasticity is defined as having increased muscle tone (MAS score ≥2) and a score of 0 on Likert scales for active function, passive function and involuntary movement, and pain score <4 on NPRS, in the relevant upper limb.
- A MAS score of 2 or more [22] in at least one of the following muscle groups: elbow flexors or pronators, wrist flexors, or finger flexors.

2.5. Exclusion criteria

- Concurrent neuromuscular junction (NMJ) diseases or any other neurological disorders that could interfere with the assessment of spasticity in the primary targeted muscle group; these include prior neuropathies as well as local joint, tendon, and intrinsic muscle disorders.
- Current treatment with drugs that affect NMJ transmission, including aminoglycosides, aminoquinolines, cyclosporine and D-penicillamine.
- Previous surgery of the affected muscles, ligaments and tendons.
- Previous BoNT-A injection within 6 months prior to study entry for any condition, or at any time in the relevant upper limb.
- Subjects likely to be treated with BoNT-A in the lower limb and other body regions during the double-blind period of the trial.
- Known hypersensitivity to BoNT-A or to any of the test materials or related compounds.
- Any medical condition (including severe dysphagia or airway disease) that may increase the likelihood of adverse events related to BoNT-A treatment. Presence of severe comorbidities such as congestive heart failure, myocardial infarction, multiple organ failure, hepatic or renal failure, or severe infection.
- Pregnant or lactating woman or premenopausal women not willing to use contraceptive measures throughout the duration of the study.

Anti-spasticity medications (e.g. baclofen) may be continued during study treatment, but only if on a stable dose.

2.6. Randomisation, data management and blinding

Randomisation will occur in a 2:1 ratio to treatment with abobotulinumtoxinA or placebo, respectively. The unbalanced randomisation ratio is included in the design for ethical purposes to ensure a maximum number of subjects are exposed to the active treatment, as it is expected to have a beneficial effect, whilst maintaining a sufficient sample size for the placebo group. Randomisation is further stratified according to the type of spasticity (symptomatic or asymptomatic). Allocation to treatment group and assignation of treatment number for drug dispensing will be managed by an interactive web response system (IWRS) using computer-generated lists organised by a statistician who is independent from the study. All data will be kept confidential and subjects will be anonymised using computer and web-based systems. Blinding of the 2:1 ratio for treatment allocation will be achieved by using two separate lists for randomisation and treatment numbering, with the ratio of initial supplies designed to be exactly balanced. Treatment resupply will be balanced to ensure that subject allocation cannot be deduced from the frequency of resupply; treatment packaging will be identical in appearance and smell.

In case emergency unblinding is required for an individual subject, for example in the event of a serious or unexpected adverse event, the investigator may break the blind by asking the IWRS to obtain the subject's treatment identification, after consultation and review of the case with the sponsor's Global Patient Safety department. In addition, one set of individually sealed code-break envelopes pertaining to the treatment received by each subject will be held by the sponsor's Global Patient Safety department.

2.7. Treatment

The target muscle group for treatment will be selected at the discretion of the treating physician and in agreement with the

Table 1
Summary of measures for assessment of spasticity and associated symptoms in the composite primary efficacy endpoint.

Functional domain and measure used	Assessment scale	
Muscle spasticity MAS [22]	0 No increase in muscle tone 1 Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension 1+ Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of motion 2 More marked increase in muscle tone through most of the range of motion, but affected part(s) easily moved 3 Considerable increase in muscle tone, passive movement difficult 4 Affected part(s) rigid in flexion or extension	MAS ≥2 indicates moderate to severe spasticity
Pain NPRS [21]	0 = no pain 1–3 = mild pain 4–6 = moderate pain 7–10 = severe pain (disabling and impacts upon movement)	NPRS ≥4 indicates appearance or reappearance of active symptoms of spasticity
Likert scale for evaluation of passive function in the relevant upper limb	"In general, how much does spasticity have an impact on the following activities of daily living and/or your rehabilitation program: hygiene (i.e. hand, nails, armpit, elbows), dressing the limb, positioning the limb, splint application or removal?" 1. No impact 2. Mild impact 3. Moderate impact 4. Severe impact	A score ≥1 indicates appearance or reappearance of passive symptoms of spasticity
Likert scale for evaluation of active function in the relevant upper limb	"In general, how much does spasticity have an impact on the following activities of daily living and/or your rehabilitation program: reaching, grasping, releasing, gripping, holding, bimanual function, manipulating objects, dexterity, fine motor skills, lifting and carrying?" 1. No impact 2. Mild impact 3. Moderate impact 4. Severe impact	A score ≥1 indicates appearance or reappearance of active symptoms of spasticity
Likert scale for evaluation of involuntary movements (including associated reactions in the relevant upper limb)	1. No involuntary movements 2. Presence of involuntary movements which have a mild impact on posture and ambulation 3. Presence of involuntary movements which have a moderate impact on posture and ambulation 4. Presence of involuntary movements which have a severe impact on posture and ambulation	A score ≥1 indicates appearance or reappearance of involuntary movements
Likert scale for global assessment of changes	"How does your patient feel compared to his/her condition at the first visit?" • Much better • Better • No change • Worse • Much worse	

MAS, modified Ashworth scale; NPRS, Numeric Pain Rating Scale.

subject from the following muscle groups in the upper limb: elbow flexors or pronators, wrist flexors or finger flexors.

Subjects will receive abobotulinumtoxinA or matched placebo by intramuscular injection into the selected target muscle group at the first visit, after all baseline assessments have been performed. Study drug is provided as a white lyophilised powder for reconstitution with 2.5 ml of preservative-free sodium chloride for injection 0.9% (200 U/ml); the complete 500 U dose will be divided among the muscles of the selected target muscle group according to the dosing instructions shown in Table 2. Electromyography, electrostimulation or ultrasound guidance are permitted, and will be documented, to facilitate accurate delivery of study injections. As study treatment is administered at the clinic by the investigator, subject compliance with treatment is not expected to be an issue.

2.8. Outcome assessments

2.8.1. Primary efficacy outcome measures

The primary endpoint was a composite endpoint developed specifically for this study to enable clinicians to distinguish between symptomatic and asymptomatic spasticity. Wherever possible, the subject will be assessed by the same evaluator at each study visit. The primary efficacy measure is the time between the initial injection of study drug (visit 1) and the visit at which

Table 2
Recommended study medication dosing regimen.

Upper limb region	Muscle	Dosing distribution	No. of injection sites	Total units	Total volume (ml)
Arm	Biceps brachii	2/3 of arm dosage	2	200	1
	Brachioradialis	1/3 of arm dosage	1	100	0.5
Forearm	Flexor carpi ulnaris	1/2 of forearm dosage	1	100	0.5
	Flexor carpi radialis	1/2 of forearm dosage	1	100	0.5
Long finger flexors	Flexor digitorum superficialis	2/5 of finger flexor dosage	Optional	Optional	Optional
	Flexor digitorum profundus	2/5 of finger flexor dosage	Optional	Optional	Optional
	Flexor pollicis longus	1/5 of finger flexor dosage	Optional	Optional	Optional
Total			5	500 U	2.5

reinjection criteria are first met. Reinjection criteria consist of increased muscle tone with a MAS score of 2 or higher in the primary targeted muscle group in addition to the appearance or reappearance of at least one of the following signs of symptomatic spasticity in the relevant upper limb, measured on the standard assessment scales defined in Table 1: pain (NPRS ≥4); presence of spasticity interfering with passive function (such as hygiene [hand, axilla, elbow, nails], dressing the limb, positioning the limb and splint application or removal; score ≥1); presence of spasticity interfering with active function (such as reaching, grasping, releasing, gripping, holding, bimanual function, manipulating objects, dexterity, fine motor skills, lifting and carrying; score ≥1); and/or presence of spasticity causing involuntary movements (score ≥1).

2.8.2. Secondary efficacy outcome measures

Subgroup analysis of the composite primary endpoint will be conducted to evaluate the median time from initial injection to reinjection criteria appearance visit in subjects with symptomatic and asymptomatic spasticity, respectively.

The time course of treatment effect will be measured by evaluating the change in muscle tone in the primary targeted muscle group from visit 1 to each subsequent visit on the MAS.

To evaluate the efficacy of abobotulinumtoxinA on upper limb motor impairment, mean change in sensorimotor upper limb function from initial injection visit to reinjection criteria appearance visit will be assessed on the Fugl-Meyer scale. This is a validated multidimensional tool for measuring motor functioning, balance, sensation and joint functioning in the upper or lower limbs of subjects with post-stroke hemiplegia [23]. To ensure consistency between different sites and investigators in applying and interpreting the Fugl-Meyer scale, a demonstration DVD developed at the Singapore study center has been distributed to all study sites, and training on the correct application of the scale has been conducted.

The use of non-drug therapy during the study will be quantified by documenting the number and duration of therapy sessions received for ULS in combination with study drug injections up to and including the subject's last visit.

Baseline characterisation of subjects will include documentation of date and type of stroke, and assessment of the severity of stroke-induced disability at visit 1 using the modified Rankin scale, where 0 represents no symptoms and 5 denotes severe disability [24].

Global assessment of change from baseline (visit 1) will be evaluated by the investigator at each subsequent visit up to, but not including, the visit when the reinjection criteria are met (Table 1).

2.8.3. Safety

The number, nature and severity of treatment-emergent adverse events disclosed through direct, non-leading questioning or spontaneous reporting will be recorded from the time that the subject gives informed consent to the subject's last study visit; adverse events will be classified as mild, moderate or severe, and likely causal relationship to study medication will be assigned by the investigator. Physical examinations and measurement of vital signs will be conducted at all visits, with any clinically significant changes recorded as adverse events.

Should an adverse event or its sequelae persist past the date of therapy discontinuation, follow-up will continue until the adverse event or its sequelae is resolved or stabilised to an acceptable level.

Any adverse events resulting in death, considered life-threatening or resulting in hospitalisation, or other serious adverse events, regardless of treatment group or suspected relationship to study treatment, are to be reported within 24 h to the sponsor's Global Patient Safety department.

2.9. Study schedule

On enrolment into the study and confirmation of eligibility criteria (visit 1), baseline assessments of acute stroke-related disease history and presenting signs and symptoms of spasticity and disability will be recorded by the investigator prior to administration of randomly assigned study treatment. Individual measures contributing to the composite primary outcome of need for reinjection will be measured at weeks 4, 6, 8, 10, 12, 16, 20, 24 and 28; all visits up to week 12 are mandatory, and visits after week 12 are required only until reinjection criteria have been met. A summary of all study observations and assessments by visit is shown in Table 3.

The subject will be considered to have completed the study at the visit when the reinjection criteria are met. If reinjection criteria are not met and the subject does not withdraw early, their last study visit will be week 28.

Subjects may be withdrawn from the study at any time at the discretion of the investigator and in the following circumstances: withdrawal of consent; occurrence of a new stroke or traumatic brain injury; failure to comply with the study protocol such that this is likely to have an adverse impact on the safety or well-being of the subject, or could jeopardise the scientific integrity of the study. The primary reason for any withdrawal will be documented in the electronic case report form (eCRF) and adverse events will be distinguished from withdrawal due to insufficient response. Upon withdrawal for any reason, subjects will be invited to attend an early withdrawal visit and will undergo, as a minimum, a safety follow-up assessment by visit or phone call within 7 days after stopping treatment.

2.10. Planned statistical analysis

As this is a preliminary pilot study intended to determine the sample size estimation for further confirmatory studies, a sample size of 42 was chosen for exploratory purposes and the study is therefore not intended to serve as the basis for definitive conclusions about safety or efficacy of abobotulinumtoxinA treatment. In addition, a planned stratification of 40–60% of subjects with symptomatic spasticity and 40–60% of subjects with asymptomatic spasticity was considered appropriate to explore the efficacy of abobotulinumtoxinA in each stratum based on the onset of reinjection criteria. Results from the study will inform a more robust sample size calculation for subsequent studies.

All randomised subjects will be included in the primary efficacy analysis (intent-to-treat population); analysis of the composite primary efficacy endpoint will also be performed in the per protocol population. All randomised subjects who received the study medication will be included in the safety analysis. There will be no interim analysis.

Statistical methods in this small pilot study will be mostly descriptive, including 95% confidence intervals (CIs), when relevant. *P*-values will be presented for exploratory purposes only; exploratory stratified analyses based on the composite primary endpoint by symptomatic spasticity status will also be performed.

For the primary endpoint analysis, median time from randomisation to reinjection criteria appearance visit will be summarised by treatment group, with 95% CIs. For subjects who have not met reinjection criteria at their last study visit (week 28/early termination), their data will be censored at the time of the last study visit. Kaplan-Meier plots of estimated probability of not having appearance of reinjection criteria will be presented by treatment group. *P*-values of log-rank tests comparing the treatment groups

Table 3
Schedule of assessments.

	Visit 1[a] First visit	Visit 2 Week 4	Visit 3* Week 6	Visit 4* Week 8	Visit 5* Week 10	Visit 6 Week 12	Visit 7* Week 16	Visit 8* Week 20	Visit 9* Week 24	Visit 10* Week 28	Early withdrawal visit*	RC visit/FU visits**
Informed consent	X											
Demographics	X											
Disease history[b]	X											
Medical and surgical history excluding post-stroke ULS	X											
Prior/concomitant medications for post-stroke ULS[c]	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications and non-drug therapies	X	X	X	X	X	X	X	X	X	X	X	X
Eligibility criteria	X											
Urine pregnancy test	X											
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X
Randomisation	X											
Study drug administration[e]	X											
MRS	X											
MAS[f]	X	X	X	X	X	X	X	X	X	X	X	X
Assessing signs of symptomatic spasticity (Likert scale):[g]	X	X	X	X	X	X	X	X	X	X	X	X
- Pain												
- Passive function												
- Active function												
- Involuntary movements												
Fugl-Meyer assessment[h]	X	X	X	X	X	X	X	X	X	X	X	
Global assessment of changes[i]		X	X	X	X	X	X	X	X	X	X	
Adverse event	X	X	X	X	X	X	X	X	X	X	X	X
Visit status	X	X	X	X	X	X	X	X	X	X	X	X

FU, follow-up; MAS, modified Ashworth scale; IM, intramuscularly; MRS, modified Rankin scale; NPRS, numeric pain rating scale; RC, reinjection criteria; ULS, upper limb spasticity.
*All visits from week 4 to week 12 are mandatory visits for all subjects participating in the study, regardless of RC status, unless the subject prematurely withdraws from the study, whatever the reason. All other study visits after week 12 are only to be performed as long as RC have not been met at the previous visit.
**When RC have been met before week 12.
[a] Study visits: the first visit must take place within 2–12 weeks post-stroke. All visits from week 4 to week 12 have a ±3-day visit window. After week 12, all study visits will have a ±1-week visit window. Following week 12, the subject's last study visit will be the visit when appearance of RC is met, week 28, or early withdrawal visit.
[b] Post-stroke upper limb spasticity: date and type of stroke.
[c] Special attention will be paid to anti-spasticity medication and dose to be maintained during the study.
[d] Will include supine heart rate and blood pressure, central body temperature and weight. Height will be recorded at the first visit only.
[e] BoNT-A (500 U) or placebo to be given IM in the UL at the first visit. The technique used to target the muscles, dose injected (for all muscles) and the number of injection sites for each muscle will be recorded.
[f] At the first visit, the investigator will select the primary targeted muscle group based on his/her clinical judgement and in agreement with the subject in one of the following muscle groups: elbow flexors or pronators, wrist flexors or finger flexors. A score ≥2 in the primary targeted muscle group at any visit after the first visit is regarded as a reinjection criterion.
[g] One or more of the following is regarded as a reinjection criterion: pain NPRS ≥4, passive function (hygiene (hand, nails, axilla, elbows), dressing the limb, positioning the limb and splint application or removal) score ≥1 on a 4-point Likert scale, active function (reaching, grasping, releasing, gripping, holding, bimanual function, manipulating objects, dexterity, fine motor skills, lifting and carrying) score ≥1 on a 4-point Likert scale, involuntary movements (including associated reactions) score ≥1 on a 4-point Likert scale in relevant upper limb.
[h] For the subject who met the RC before week 12, Fugl-Meyer assessment will not be performed at the subsequent visit(s).
[i] Assessed by the investigator using a 5-point Likert scale. For subjects who meet the reinjection criteria before week 12, global assessment will not be performed after the visit when the RC have been met.

will be presented for exploratory purposes only and will not provide a formal statistical comparison.

Descriptive statistics including 95% CIs will be used to present secondary efficacy endpoints, with exploratory *P*-values presented where possible. If the number of subjects is sufficient, median time from randomisation to reinjection criteria appearance visit will be analyzed using the same methodology as for the primary endpoint in subgroups defined by symptomatic spasticity status. Other continuous endpoints will be compared between treatment groups using analysis of covariance (ANCOVA; adjusting for the score at the first visit) or ranked ANCOVA, depending on the data distribution.

2.11. Study management and data monitoring

All study reporting will be by electronic data capture. Accepted standard procedures for auditing of the study implementation and verification of all source data and documents, data monitoring and eCRF completion, monitoring, collection and storage will be followed as detailed in the protocol. Consent for subjects' medical records to be viewed by sponsor-authorised personnel and relevant authorities is included in the subject consent form.

3. Ethics and dissemination

3.1. Ethics

The study has received approval from the independent ethics committee/institutional review board in each participating center, and will be conducted in compliance with informed consent regulations, the Declaration of Helsinki and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. Written informed consent will be obtained prior to the subject entering the study (before initiation of any study-related procedure and administration of study treatment); the investigator, or a

person designated by the investigator, will explain the nature, purpose, benefits and risks of participation in the study, and the consent form will be personally signed and dated by the subject or by the subject's legally acceptable representative.

3.2. Dissemination

The results of the trial will be disseminated at international scientific congresses and through peer-reviewed publications. Authorship will be based on the criteria defined by the International Committee of Medical Journal Editors [25], and due acknowledgement will be given to all individuals/organisations involved in the funding or conduct of the study, including medical writers and statisticians, subject to the consent of each individual and entity concerned.

3.3. Discussion

Three upper limb randomised controlled trials provide evidence that BoNT-A administered within the first 3 months after stroke may provide sustained improvement in muscle tone as measured using the MAS [15,19,20]. In a single-blind, randomised pilot study involving 18 post-stroke subjects with MAS scores of 1 or 2, early treatment with incobotulinumtoxinA (Xeomin®, Merz Pharma, Germany) improved finger flexor stiffness for at least 6 months, with the improvements attributed to reduced development of contracture [19]. In another phase II pilot study, 30 subjects received either BoNT-A (onabotulinumtoxinA, Botox®, Allergan, USA) at prespecified reductions to the standard dose or placebo, within 3 weeks of stroke onset. Although there was no overall difference in improvement of arm function between groups, subgroup analysis revealed that subjects with more severe functional impairment might benefit from early injection of low-dose BoNT-A [20].

The largest trial to date, the Asia Botulinum Toxin-A Clinical Trial Designed for Early Post-stroke Spasticity (ABCDE-S) study (NCT00234546), evaluated changes in upper limb muscle tone following one injection cycle of abobotulinumtoxinA or placebo in 182 subjects with MAS score $\geq$1 within 2–12 weeks of stroke. Muscle tone remained significantly decreased by the end of the 24-week study [15]. The study also demonstrated that abobotulinumtoxinA reduced spasticity-related pain after 4 and 24 weeks of follow-up. Of note, there have been two similar studies on BoNT-A for early lower limb post-stroke spasticity and spasticity from non-progressive brain lesions (e.g. traumatic brain injury and hypoxia) [26,27].

The ONTIME study will be the second to evaluate abobotulinumtoxinA in the early treatment setting, but will differ in three important aspects to the ABCDE-S study [15]. Firstly, there are notable differences between the primary endpoints used in these two studies. The ONTIME study will employ a composite primary endpoint developed to enable clinicians to distinguish between symptomatic (disabling) and asymptomatic spasticity. This composite endpoint combines the measure of increased muscle tone (MAS) with the evaluation of functional elements (active function, passive function, involuntary movement and pain). The use of composite indices has been implemented in various acute stroke trials [28–33], as it is recognised that one index may not be as powerful as another, but put together, may lead to better outcome evaluation. In particular, a *post hoc* analysis was performed in this regard to evaluate vascular outcomes after stroke, with the reasoning that various vascular events occur after stroke and so a composite endpoint was required [28]. In the ONTIME study, not every patient will have the same symptoms, but put together as a composite endpoint, especially considering the homogeneous populations (Asian patients with early onset post-stroke spasticity receiving the same dose of BoNT-A in the affected upper limb), the desired outcomes may reach impactful levels.

Secondly, as symptomatic spasticity is more likely to develop in more severely affected patients [13], only subjects with moderate to severe spasticity (MAS $\geq$ 2) will be included in the ONTIME study, to ensure that meaningful functional gains are detected. This represents a patient population with more severe spasticity than subjects included in the ABCDE-S study. Furthermore, a longer follow-up (up to 28 weeks) is planned to allow adequate time to follow and document the appearance or reappearance of post-stroke spasticity symptoms following BoNT-A injection.

Results from this pilot study will facilitate the design and sample size calculation of further confirmatory studies and are expected to provide useful insights into the optimal delivery of post-stroke patient management, including timing of BoNT-A therapy and duration of follow-up regimens.

4. Trial status

Recruitment to the ONTIME pilot study began in December 2014 and was completed in September 2015 (final data collection for the primary outcome measure).

Authors' contributions

KHK, JB, HB, PM, KJG, WK, RR all contributed to the conception and design of the ONTIME protocol. KHK, JB, HB, PM, KJG, WK, RR all contributed to the critical revision of this manuscript for intellectual content, provided final approval of the version to be published, and accept accountability for all aspects of the work.

Declaration of conflicting interests

RR, KHK, KJG and WK have received consultancy fees from Ipsen Pharma. JB, HB and PM are full-time employees of Ipsen Pharma.

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Trial registration

ClinicalTrials.gov number NCT02321436.

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