

TITLE PAGE

Protocol Title: A phase III study (a placebo controlled, randomized, double-blind comparative study and an open-label, uncontrolled study) to evaluate the efficacy and safety of GSK1358820 in patients with post-stroke upper limb spasticity

Protocol Number: 207660

Short Title: A phase III study to evaluate the efficacy and safety of GSK1358820 in patients with post-stroke upper limb spasticity

Compound Number: GSK1358820

Sponsor

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Regulatory Agency Identifying Number(s):NA

Approval Date: 04-APR-2017

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Date

The IMMS document approved is as follows:

Unique ID :

System Version:

Effective Date:

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1. SYNOPSIS

Protocol Title: A phase III study (a placebo controlled, randomized, double-blind comparative study and an open-label, uncontrolled study) to evaluate the efficacy and safety of GSK1358820 in patients with post-stroke upper limb spasticity

Short Title: A phase III study to evaluate the efficacy and safety of GSK1358820 in patients with post-stroke upper limb spasticity

Rationale:

GSK1358820, botulinum toxin type A (hereafter referred as the product), is sterile, purified type A botulinum neurotoxin complex. Intramuscularly injected botulinum neurotoxin shows muscle relaxant effects by blocking the neuromuscular junction and inhibiting release of acetylcholine, a neurotransmitter. Since the approval of the product for strabismus and blepharospasm in US in 1989, the product is licensed for the treatment of various diseases, which respond to the muscle relaxant effects in more than 90 countries (as of Apr 2017).

In Japan, the product is licensed with 8 indications as an ethical drug so far: blepharospasm as a first indication in Oct 1996, followed by “hemifacial spasm” in Jan 2000, “spasmodic torticollis” in Jun 2001, “talipes equinus associated with lower limb spasticity in pediatric patients two years of age and older with cerebral palsy” in Feb 2009, “upper limb spasticity” and “lower limb spasticity” in Oct 2010, “severe primary maschalephidrosis” in Nov 2012, and “strabismus” in Jun 2015. For “upper limb spasticity,” 240 units of the product is approved as a maximum dose per administration. In US, as a maximum dose per administration, 400 units of injection of the product have been approved for the treatment of upper limb spasticity in adult patients in 2015; therefore, the authorized dose of the product between US and Japan is different.

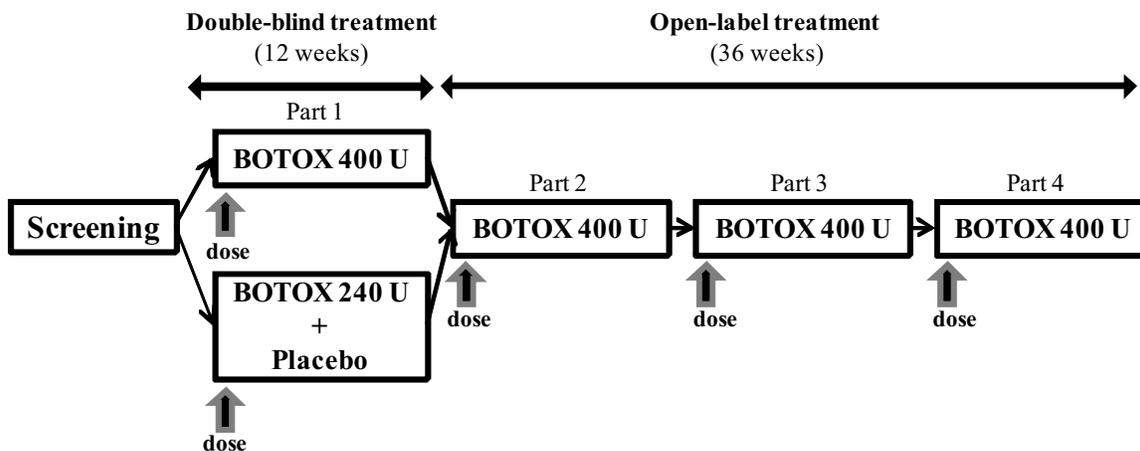
This study is a multicenter, double blind, placebo controlled phase III domestic study and aims to evaluate the efficacy and safety of 400 units of the product in patents with post-stroke upper limb spasticity. The study was planned to increase the maximum dose per administration in Japan to 400 units from 240 because the treatment with 240 units of the product, a maximum dose per administration, is considered to be insufficient in some patients with post-stroke upper limb spasticity.

Objectives and Endpoints:

| Objectives | Endpoint(s) |
|---|--|
| Primary | |
| To evaluate the efficacy of the injections of 400 units of the product at Week 6 (finger/ wrist flexors: 240 units, elbow flexors: 160 units), comparing to that of 240 units (finger/ wrist flexors: 240 units, elbow flexors: placebo). | The responder rate : The rate of the subjects that Modified Ashworth Scale (MAS) score was reduced at least 1 from baseline in the elbow flexors. |
| Secondary | |
| To evaluate the efficacy of 400 units of the product, comparing to 240 units of the product | <ul style="list-style-type: none"> • The responder rate of MAS score from baseline in the finger, thumb and wrist flexors • Changes in MAS score from baseline in the finger, thumb, wrist and elbow flexors • Changes in Disability Assessment Scale (DAS) from baseline |
| To evaluate the safety and tolerability of the product of 400 units, comparing to 240 units of the product/ To evaluate the safety and tolerability of 400 units of the product | <ul style="list-style-type: none"> • Adverse events • Physical examinations • Clinical laboratory tests (haematology, blood biochemistry, urinalysis) • Vital signs (heart rate, blood pressure, body temperature) |
| Exploratory | |
| To evaluate the efficacy of 400 units of the product | <ul style="list-style-type: none"> • Changes in MAS score from baseline in finger, thumb, wrist, elbow, pronation of the forearm and shoulder flexors |
| To evaluate the other efficacy of the product of 400 units, comparing to 240 units of the product/ To evaluate the other efficacy of 400 units of the product | <ul style="list-style-type: none"> • Changes in Numeric Rating Scale (NRS) for pain from baseline • Changes in other items of DAS from baseline • Clinical Global Impression of Change (CGI) of functional disability by a investigator • CGI of functional disability by a patient • Time to patient-reported onset of spasticity symptom relief • Patient-reported benefit of injection • Time to qualification for retreatment |
| To evaluate neutralizing antibody production | <ul style="list-style-type: none"> • Testing for neutralizing antibody |

Overall Design:

This study is a 48-week multicenter, phase III study (a placebo controlled, randomized, double-blind comparative study and an open-label, uncontrolled study) to evaluate the efficacy and safety of the product in patients with post-stroke upper limb spasticity. The study period is up to 52 weeks, consisting of a screening phase up to 4 weeks, minimum 12-week blind phase (Part 1), maximum 36-week open-label phase (12 weeks per cycle with maximum 3 treatment phases: Part 2, Part 3 and Part 4).

**Number of Participants:**

Approximately 120 subjects (approximately 60 in each group) will be randomized to obtain an evaluable subject sample of approximately 100 at Week 48 as subjects with completion of the study.

Treatment Groups and Duration:**Screening Phase (Day -28~Day -1)**

Evaluation and screening tests will be performed 28 to 7 days (± 3 days) before initial injection (Day 1) as a starting point. The investigator will decide which arm to be injected during screening phase.

Blind Phase (minimum 12 Weeks): Placebo Controlled, Randomized, Double Blind Design

Subjects who meet the inclusion criteria will be randomly assigned 1:1 to either the 400 or the 240 units group.

- In the 400 units group, a total of 240 units of the product will be injected into the muscles that act on the finger (including thumb flexors) and wrist flexors, and a total of 160 units into the muscles that act on the elbow flexors; a total of 400 units of the product will be injected.
- In the 240 units group, a total of 240 units of the product will be injected into the muscles that act on the finger (including thumb flexors) and wrist flexors. Placebo will be injected into the muscles that act on the elbow flexors. A total of 240 units of the product will be injected.

If the total dose for the muscles that act on the finger and wrists flexors is ensured by 240 units, and 160 units for the muscles that act on the elbow flexors, the dose can be adjusted at an investigator's discretion based on the subject's symptoms.

Open-Label Phase (maximum 36 Weeks): Uncontrolled, Open-Label Design

The product of 400 units will be injected in both groups. The product can be injected up to 3 times after completion of Part 1 in the blind phase. In the open-label phase, subjects whom the investigator considers eligible for the injections will be treated. The next injections cannot be performed until the eligibility of the subject has been confirmed by the investigator.

In the open-label phase, the muscle to be injected and the dose will be decided by the investigator based on the patient's symptoms, and a total dose of 400 units of the product will be injected in a divided dose. For the muscles that the investigator considers unnecessary to be treated, an injection may be skipped. The involving muscle and the dose do not have to be the same each time always.

Injection Criteria in and after Part 2 in the Open-Label Phase

In the open-label phase (Part 2, Part 3, and Part 4), only the subjects whom the investigator considers eligible for the study will be injected. The eligibility is evaluated at a study visit after Week 12 (V5). If a subject does not meet the criteria at V5, the eligibility is evaluated at QRV (Qualification for Retreatment Visit). Subjects are considered to be eligible if following criteria are all satisfied:

- 1) At least 12 weeks (84 days) have passed since the preceding dose
- 2) Among the finger, wrist or elbow flexors, 2 flexors have at least 2 on the MAS (except only the finger and wrist flexors of 2 on the MAS)
- 3) Subject who request the injections
- 4) Subjects whom a investigator considers an injection of 400 units of the product is appropriate
- 5) Subjects who are considered to remain freedom from unacceptable safety concerns (including potential for serious adverse events, laboratory data, electrocardiogram or pulmonary function test value) due to the injections of 400 units of the product
- 6) Subjects who have not experienced serious adverse events (SAE) associated with the injections of the product

If a subject meets above criteria at V5 or QRV, the following items are confirmed before V1 injection:

- Body weight \geq 40 kg
- Women of childbearing potential who have negative pregnancy test results in urine

2. SCHEDULE OF ACTIVITIES (SoA)

Compliance with the protocol (including the list of the study conduct schedule) is important and required to conduct the study. Therefore, exemption or discharge cannot be allowed, except but emergency safety concerns arise.

The study operation schedule is shown on [Table 1](#). Examples of injections in the open-label phase based on evaluation of eligibility for injection are shown on [Figure 1](#), [Figure 2](#), [Figure 3](#), and [Figure 4](#).

Table 1 SCHEDULE OF ACTIVITIES (SoA)

| Visit | Screening ^a SV | Blind phase If a subject meets the eligibility at V5/ QRV, the subject will move forward to the open-label phase | | | | | | Open-label phase If a subject meets the eligibility at V5/QRV, the subject will move forward to the next treatment phase | | | | | | Completion visit Final Visit |
|--|------------------------------|--|----|----|----|--|---|--|----|----|----|--|---|---------------------------------------|
| | | Part 1 | | | | | Eligibility evaluation ^b | Part 2/Part 3/ Part 4 | | | | | Eligibility evaluation ^b | |
| | | V1 (Day 1) | V2 | V3 | V4 | V5 ^c (Eligibility evaluation) | QRV | V1 | V2 | V3 | V4 | V5 ^d (Eligibility evaluation) | QRV | |
| Time from initial injection (Day 1) (Weeks) | — | 0 | 2 | 4 | 6 | 12 | Allowable Week 16 to 36 ^e | — | — | — | — | — | Allowable Week 24 to 36 ^e | 48/ Withdrawal |
| Time from injection day in each treatment phase (Weeks) | — | 0 | 2 | 4 | 6 | 12 | 16/ 20/ 24/ 28/ 32/ 36 | 0 | 2 | 4 | 6 | 12 | 16/ 20/ 24 | - |
| Acceptable visit windows (days) | — | ±4 | ±4 | ±4 | ±4 | +4 ^f | ±14 ^g | +4 | ±4 | ±4 | ±4 | +4 ^f | ±14 ^g | ±4 |
| Written informed consent | X ^h | | | | | | | | | | | | | |
| Randomization | | X ⁱ | | | | | | | | | | | | |
| Injections | | X | | | | | | X | | | | | | |
| Evaluation of eligibility | | | | | | X | X | | | | | X | X | |
| Inclusion/exclusion criteria ^j | X | X ⁱ | | | | | | | | | | | | |
| Subject demography | X | | | | | | | | | | | | | |
| MAS ^k | X | X ⁱ | X | X | X | X | X | X ^{l,t} | X | X | X | X | X | X |
| NRS ^l | | X ⁱ | X | X | X | X | X | X ^{l,t} | X | X | X | X | X | (X) ^r |
| DAS | | X ⁱ | X | X | X | X | X | X ^{l,t} | X | X | X | X | X | (X) ^r |
| CGI by a investigator | | | X | X | X | X | | | X | X | X | X | | (X) ^r |
| CGI by a patient | | | X | X | X | X | | | X | X | X | X | | (X) ^r |
| Time to patient-reported onset of spasticity symptom relief | | | X | | | | | | X | | | | | |
| Patient-reported benefit of injection | | | | X | X | X | | | | X | X | X | | (X) ^r |
| Physical examination (complete version) | X | | | | | | | | | | | | | |
| Physical examination (simplified version) | | X ⁱ | | | | X | | X ^{l,t} | | | | X | | X |
| Medical history | X | X ⁱ | | | | | | | | | | | | |
| Vital signs ^m | X | X ⁱ | | | | X | | X ^{l,t} | | | | X | | X |
| Height | X | | | | | | | | | | | | | |
| Body weight | X | | | | | | | X ⁱ | | | | | | |
| Electrocardiogram | X | | | | | | | X ⁱ | | | | | | |
| Pregnancy test ⁿ | X | X ⁱ | | | | | | X ⁱ | | | | (X) ^r | | X |
| Laboratory test ^o | X | | | | | X | | | | | | X | | X |
| Adverse events ^p | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications/therapies | X | X ⁱ | X | X | X | X | X | X ^{l,t} | X | X | X | X | X | X |
| Testing for neutralising antibodies ^q | X | | | | | X | | | | | | | | X |

- a. Test items for screening must be performed 1 weeks before Day 1 visit (± 3 days).
- b. Eligibility evaluation (Qualification for Retreatment Visit: QRV) will be performed at V5 as a starting point if a subject does not meet the criteria only. The evaluation is performed at a 4-week interval, V5 as a starting point, The QRV when a subject meets the criteria will be a same day as the injection in the next treatment period (refer to [Figure 1](#), [Figure 2](#), [Figure 3](#), [Figure 4](#)).
- c. If a subject is evaluated to meet the eligibility for the injection in the blind phase at V5, the subject will move forward to Part 2 in the open-label phase (Namely, V5 in Part 1 and V1 in Part 2 is a same day). If the subject does not meet the eligibility, QRV will be performed 4 weeks later, at V5 as s starting point.
- d. If a subject is evaluated to meet the eligibility at V5 in the open-label phase, the subject will move forward to the next treatment phase (V5 and V1 in the next treatment phase is a same day). If the subject does not meet the eligibility, QRV is performed 4 weeks later, V5 as a starting point. If V5 in Part 4 is at Week 48 after initial injection, V5 will be considered to be completion visit (FV). However, for the testing items, pre-scheduled tests at V5 and neutralizing antibody tests will be performed. If V5 in Parts 2 and 3 is performed at Week 36 or later, after completion of V5, completion visit will be performed at Week 48.
- e. QRV is allowable to perform from initial injection to Week 36. Eligibility evaluation (QRV) will not be performed after Week 36.
- f. V5 must be performed at least 84 days after V1.
- g. The acceptable visit windows will be -14 to +4 days if QRV is performed at Week 36.
- h. Must be performed earlier than any other procedures
- i. Must be performed before injection of the product
- j. For inclusion/exclusion criteria, the items to be observed are different between screening phase and Day 1. For details, refer to [6.1](#). and [6.2](#).
- k. For MAS evaluation, the items to be evaluated differ depending on the treatment phase. For details, refer to [9.1.1.1](#).
- l. MAS evaluation will be followed by NRS evaluation. For NRS evaluation, items to be evaluated differ. For details, refer to [9.1.1.2](#).
- m. Body temperature, heart rate, and blood pressure will be measured as vital signs.
- n. Women of childbearing potential will be only performed. Serum hCG pregnancy test must be performed at screening, and urine hCG pregnancy test after randomization. The tests can be performed beyond the protocol specifications if a investigator considers to be necessary.
- o. For laboratory test items, refer to [12.2](#). Attachment 2. Fasting is not required for blood collection.
- p. Adverse events and serious adverse events collection period will be from the initial injection day (Day 1) to completion visit (FV).
- q. Neutralizing antibody testing is performed 3 times in each subject. The first test will be performed in screening phase, the second is at QRV in the blind phase, and the third is at completion visit.
- r. A subject who withdraws the study before 12 weeks after last injection will be performed.
- s. Perform if V5 in Part 4 is at Week 48 after initial injection
- t. Not necessary to perform doubly as V1 assessment if the same assessment is performed at V5

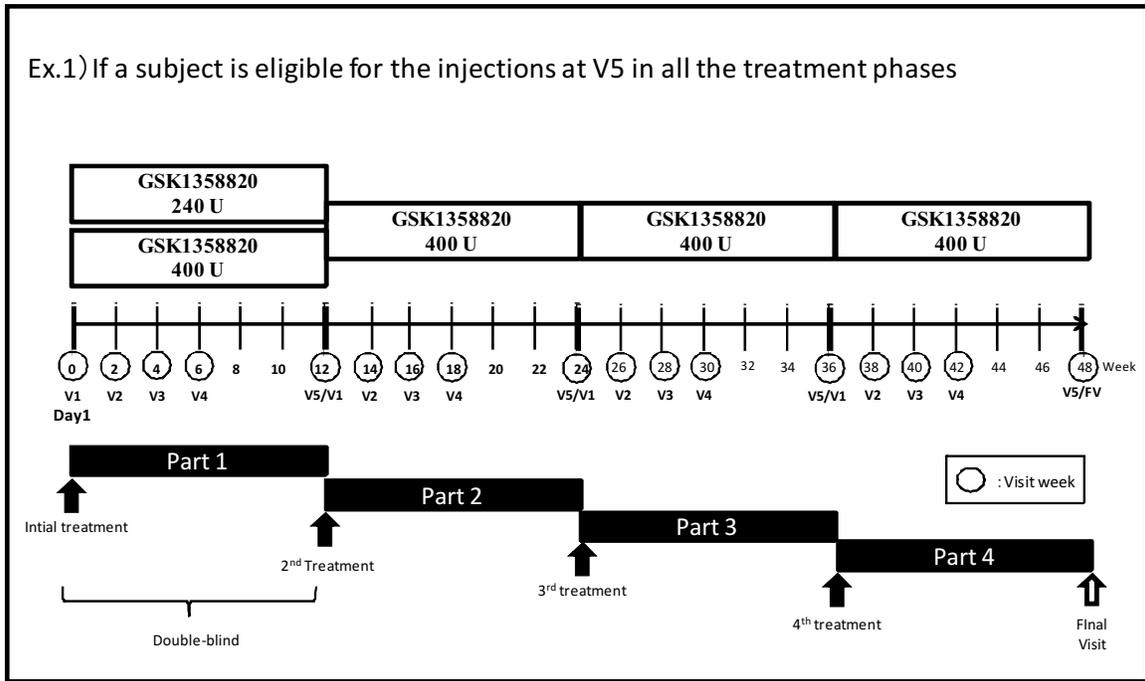


Figure 1 Eligibility Evaluation in the Open-Label Phase (Example 1)

If a subject is eligible for the injections at V5 in all the treatment phases, 4 injections will be performed throughout the study. Week 48 visit is performed also as a completion visit.

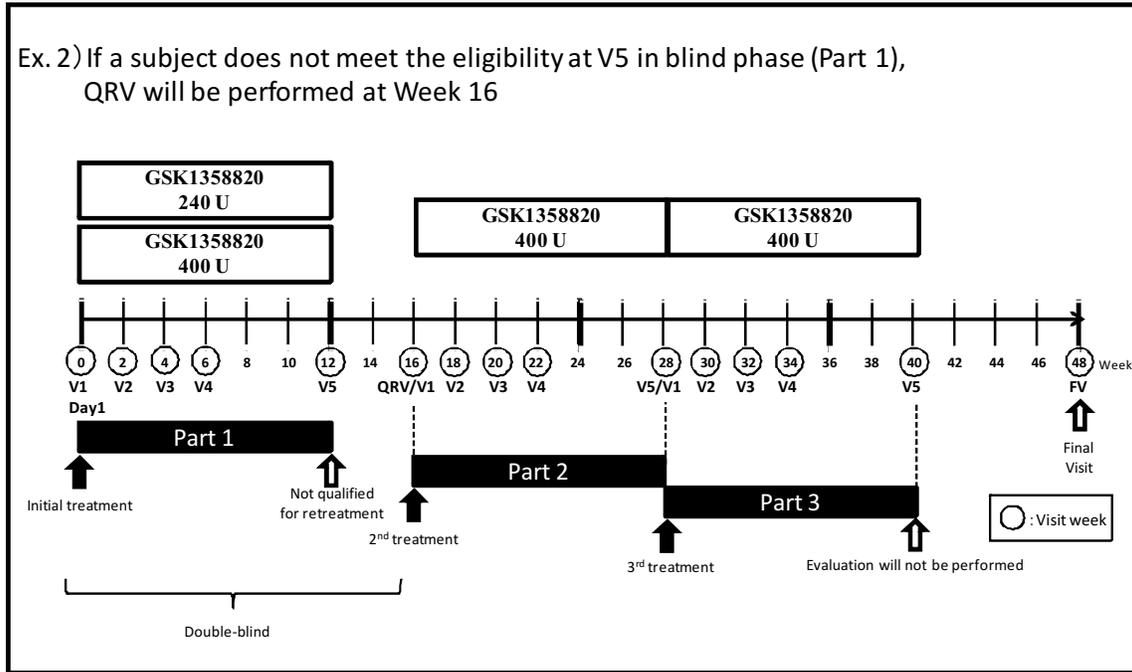


Figure 2 Eligibility Evaluation in the Open-Label Phase (Example 2)

If a subject does not meet the eligibility at V5 in blind phase (Part 1), QRV will be performed at Week 16. V5 in Part 3 is at Week 40, therefore, eligibility evaluation will not be performed. After V5 at Week 40, FV will be performed at Week 48.

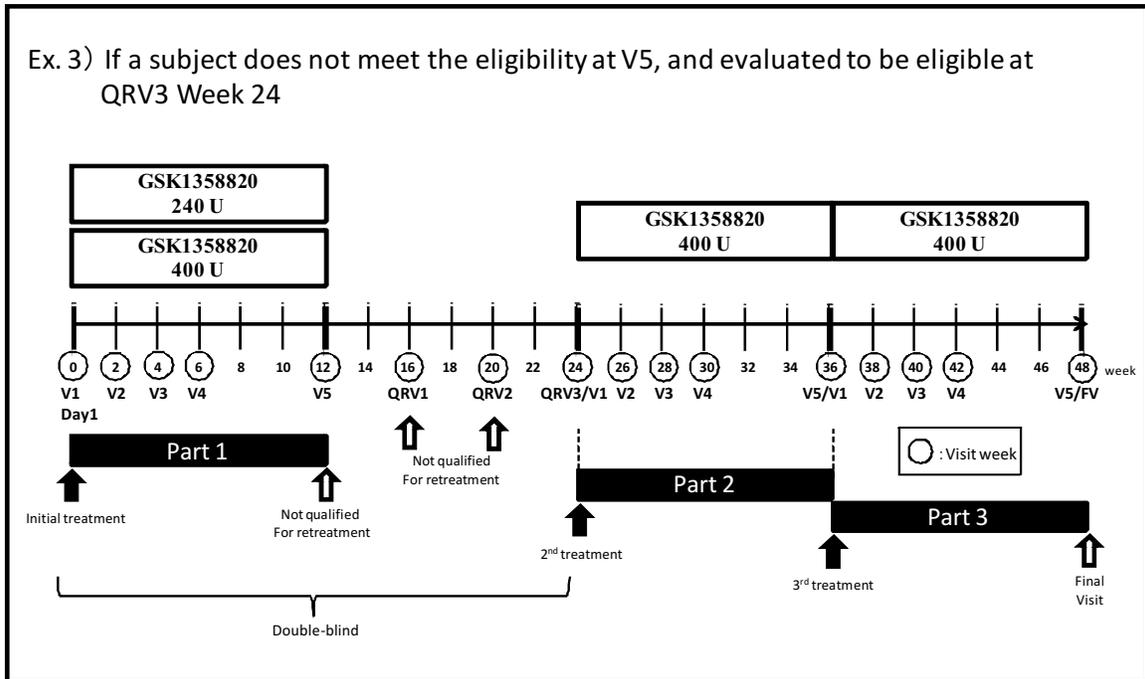


Figure 3 Eligibility Evaluation in the Open-Label Phase (Example 3)

If a subject does not meet the eligibility at V5 in the blind phase (Part 1), QRV will be performed until the eligibility have confirmed at 4 weeks intervals, at V5 as a starting point. If a subject is evaluated to be eligible at QRV3 Week 24, the injections in Part 2 will be performed on the same day as QRV3. V5 in Part 3 is in Week 48, therefore, at V5, completion visit (FV) will be also performed.

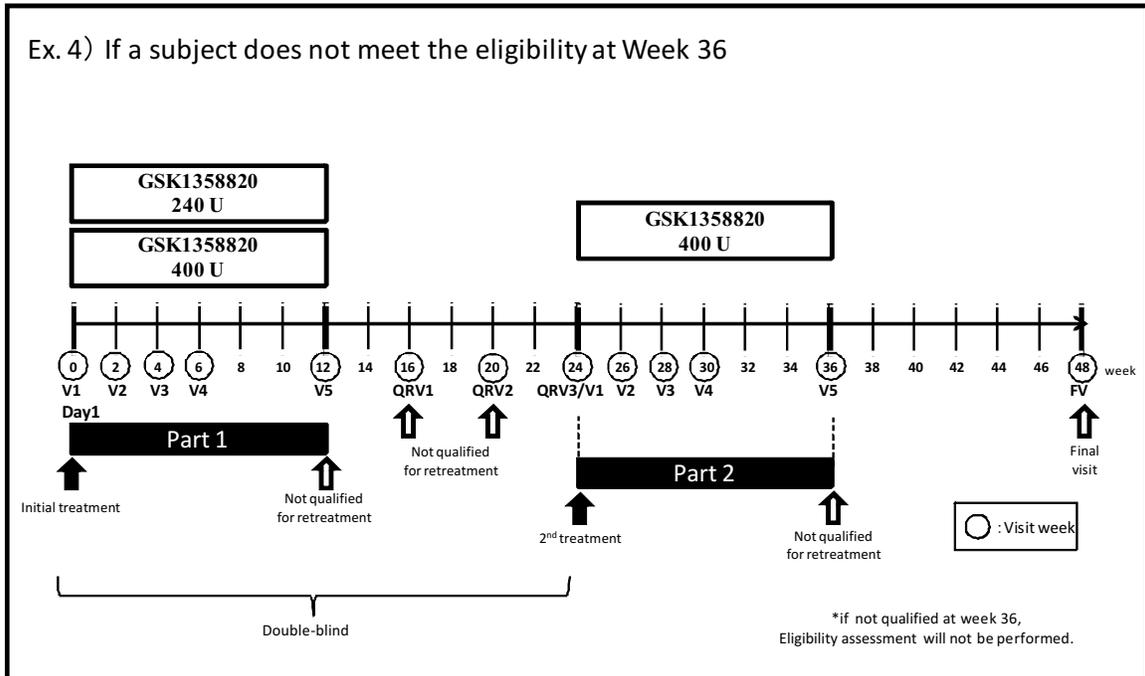


Figure 4 Eligibility Evaluation in the Open-Label Phase (Example 4)

QRV in Part 2 is Week 36, and if a subject does not meet the criteria, subsequent injections will not be performed, and Week 48 completion visit will be performed.

3. INTRODUCTION

3.1. Study Rationale

GSK1358820, botulinum toxin type A (hereafter referred to as the product) is sterile, purified type A botulinum neurotoxin complex. Intramuscularly injected botulinum neurotoxin shows muscle relaxant effects by blocking the neuromuscular junction and inhibiting the release of acetylcholine, a neurotransmitter. Since the approval of the product for strabismus and blepharospasm in US in 1989, the product is licensed for the treatment of various diseases, which respond to the muscle relaxant effects in more than 90 countries (as of Apr 2017).

In Japan, the product is licensed with 8 indications as an ethical drug so far: blepharospasm as first indication in Oct 1996, followed by “hemifacial spasm” in Jan 2000, “spasmodic torticollis” in Jun 2001, “talipes equinus associated with lower limb spasticity in paediatric patients two years of age and older with cerebral palsy” in Feb 2009, “upper limb spasticity” and “lower limb spasticity” in Oct 2010, “severe primary maschalephidrosis” in Nov 2012, and “strabismus” in Jun 2015. For “upper limb spasticity,” 240 units of the product is approved as a maximum dose per administration.

This study is a multicenter, double blind, placebo controlled phase III domestic study in patients with upper limb spasticity and aims to confirm the efficacy and safety of 240 units of the product for post-stroke upper limb spasticity. The information of 400 units of the product in the study is expected to provide beneficial information because the treatment with 240 units of the product with a maximum dose per administration is considered to be insufficient in some patients with post-stroke upper limb spasticity.

3.2. Background

Spasticity is a movement disorder that is characterized by increased myotatic reflex and is regarded as one of positive signs of the upper motor neuron signs (Kagamihara, 2012; Lance, 1980). Spasticity is caused by central nerve system injuries such as stroke, traumatic brain injury, or spinal cord injury and chronic neuropathies such as cerebral palsy or multiple sclerosis, etc. Abnormal postures of the upper limbs due to spasticity include thumb refraction, a clenched fist deformity, flexion of the wrist flexors, pronation of the forearms, flexion of the elbow flexors, and adduction/inner rotation of the shoulder flexors (Gracies, 2003; Kinoshita, 2015).

Spasticity hampers rehabilitation therapy. In addition, limitation of flexors range of motion and persistent pain hinder from caregiving and decrease activity in daily life (Grazko, 1995); therefore, many of patients with stroke require treatments to ameliorate their dysfunction.

For the treatments of spasticity, rehabilitation therapy, oral medications, phenol blocks, and baclofen injections were used until botulinum therapy has been approved as a national health insurance coverage. These treatments were commonly challenging because of lack of effects, difficult procedures, or invasive interventions. Subsequently, in Oct 2010, the product was approved as a botulinum treatment for upper and lower limb spasticity in Japan. Since then, botulinum toxin has been used for the treatment of spasticity (Ohsawa, 2013). According to the “Japanese Guidelines for the Management of Stroke” (initial version in 2009, revised in 2015) (Ogawa, 2015; Shinohara, 2009), which was issued by the Japan Stroke Society, botulinum therapy is recommended for the treatment of spasticity as Grade A, and is considered to be effective for relief of upper limb spasticity, increase of range of motions in flexors, and reduction of the amount of assistance on daily life.

In Japan, upper limb spasticity, a domestic phase II study involving the finger, wrist, and elbow flexors was performed from Dec 2001 through Mar 2003, and a domestic phase III study involving the finger and wrist flexors from May 2007 through Dec 2008. Consequently, the product was approved for the treatment of upper limb spasticity with a maximum dose of 240 units per administration in Oct 2010.

However, subsequently, the injections of the product at 240 units were found to be insufficient for the involving muscles because patients with extensive upper limb spasticity require dose adequate to inject into many of the involving muscles. Therefore, many medical institutions requested us to increase the maximum dose per administration of the product. Moreover, the specified drug-use survey from Jun 2011 through Apr 2014 identified that approximately 39% of the patients who use the product for upper limb spasticity were injected more than 240 units, a maximum dose per administration. The results suggest high patient needs for an increase of the maximum dose per administration of the product.

In US, as a maximum dose per administration, 400 units of injections of the product have been approved for the treatment of upper limb spasticity in adult patients in 2015; therefore, the authorized dose between US and Japan is different.

Based on these background, the study was planned to evaluate the efficacy and safety of 400 units of the product for upper limb spasticity in order to increase the maximum dose per administration to 400 units.

The study was planned based on the regulatory advice by the Pharmaceuticals and Medical Devices Agency (PMDA).

3.3. Benefit/Risk Assessment

For details of the known and anticipated benefit/risk and rationally expected adverse events are shown on the Investigator's Brochure (IB) and package insert.

3.3.1. Risk Assessment

| Important identified risks | Reports suggesting risks/ Outlines of rationale | Measures for risk minimization |
|--|--|--|
| Investigational product :GSK1358820 | | |
| Hypersensitivity | Serious and/or immediate hypersensitivity reactions (anaphylaxis, serum sickness, urticarial, soft tissue edema, or dyspnea, etc.) have been rarely reported. | Patients who previously experienced allergic reactions due to botulinum toxin type A, an additive agent of sodium chloride, or human serum albumin are excluded from enrolment. Upon written informed consent process, subjects will be explained that any urticarial, swelling face, throat swelling, wheezing, dizziness, or dyspnoea should contact their investigator. |
| Pre-existing neuromuscular disorder | Patients with neuromuscular junction diseases (myasthenia gravis, Lambert-Eaton myasthenic syndrome etc.) may increase the sensitivity to the product, resulting in excessive muscular weakness. | For patients with myasthenia gravis, Eaton-Lambert syndrome (ELS), amyotrophic lateral sclerosis, or a serious disease and who use a concomitant drug (s) which may inhibit neuromuscular function, exclusion criteria will be set, and those patients will be excluded from enrolment in the study (refer to 6.2.1). |
| distant spread of toxin | Adverse drug reactions in the remote muscles, except but the injected site, have been rarely reported. The adverse drug reactions include muscular weakness, constipation, dysuria, swallowing difficult, and non-accidental entering of food or fluid in the lungs not via the stomach, but the trachea (pneumonia may occur). The patients who received the product at a higher dose are considered likely to have increased risks for these adverse drug reactions. | In this study, a high dose of 400 units of the product will be injected. Therefore, the subjects will be followed up after 2, 4, 6, and 12 weeks of injection. The safety of the subjects will be observed carefully. Use of at least one of the following guide tools (electromyogram, electrical stimulator, or ultrasonography) will be essential in the blind phase to ensure identification of the exact site of injection. |

| Important identified risks | Reports suggesting risks/ Outlines of rationale | Measures for risk minimization |
|--|---|--|
| Immunogenicity, drug resistance, antibody production | The important cause of neutralizing antibody production has not been fully clarified. A few studies suggested that the injection of the product at short intervals or at a high dose may lead to increased rate of antibody production[Jankovic, 2006; Klein, 2002]. Neutralizing antibody production against botulinum toxin type A may lead to inactivation of the biological activity of the product, resulting in decreased therapeutic effects of the product. | In this study, patients who were considered likely to have neutralizing antibody production based on the previous treatment experience of botulinum toxin type A will be excluded from enrolment in the study (Exclusion Criteria 6.2.1). In addition, treatment schedule in the study was set to ensure at least a 12-week dosing interval. |
| Other (If applicable) | | |
| Medication error (preparation with lidocaine) | One fatal case due to anaphylaxis has been reported. In this case, the patient died after 100 units of an injection of the product that prepared inappropriately with 5 mL of 1% lidocaine. The causal relationship of death to the product and lidocaine, or both has been unknown. | In this study, the product will be prepared appropriately with 0.9% normal saline. The preparation method will be described on the study reference manual (SRM). |

3.3.2. Benefit Assessment

In patients with post-stroke upper limb spasticity, currently, the product is approved to inject up to 240 units per administration in Japan. However, in patients with extensive upper limb spasticity, the treatment effects of the product is presumed to lack because of the dose limitation.

In US, the efficacy and safety of the product up to 400 units per dose for patients with upper limb spasticity is confirmed, and the clinical use of the product has been approved. The injections of 400 units of the product in this study are expected to increase injectable sites and enhance the treatment effects in Japanese patients with upper limb spasticity, who did not have great benefits from 240 units of the product.

If a subject is assigned to the 240 units group in Part 1 and meets the eligibility criteria for injection in the open-label phase, 400 units of the product will be injected in and after Part 2. Therefore, all the subjects who participate in this study are given the opportunity to receive 400 units of the product (Refer to “[5. STUDY DESIGN](#)”).

3.3.3. Overall Benefit:Risk Conclusion

The known potential risks in the product is justified by the benefits which would provide for the patients with post-stroke upper limb spasticity, given the safety measures to minimize risks in subjects who enrol in the study.

4. OBJECTIVES AND ENDPOINTS

| Objectives | Endpoint(s) |
|--|--|
| Primary | |
| To evaluate the efficacy of injection of 400 units of the product at Week 6 (finger/ wrist flexors: 240 units, elbow flexors: 160 units), comparing to that of 240 units (finger/ wrist flexors: 240 units, elbow flexors: placebo). | The rate of the subjects that Modified Ashworth Scale (MAS) score was reduced at least 1 from baseline in the elbow flexors (the responder rate). |
| Secondary | |
| To evaluate the efficacy of 400 units of the product, comparing to 240 units of the product. | <ul style="list-style-type: none"> • The responder rate of MAS score from baseline in finger, thumb and wrist flexors • Changes in MAS score from baseline in finger, thumb, wrist, elbow, pronation of forearms and shoulder flexors • Changes in Disability Assessment Scale (DAS) from baseline |
| To evaluate the safety and tolerability of the product of 400 units, comparing to 240 units of the product/ To evaluate the safety and tolerability of 400 units of the product. | <ul style="list-style-type: none"> • Adverse events • Physical examinations • Clinical laboratory tests (haematology, blood biochemistry, urinalysis) • Vital signs (heart rate, blood pressure, body temperature) |
| Exploratory | |
| To evaluate the efficacy of 400 units of the product | <ul style="list-style-type: none"> • Changes in MAS score from baseline in finger, thumb, wrist, elbow, pronation of the forearm and shoulder flexors |
| To evaluate the other efficacy of the product of 400 units, comparing to 240 units of the product/ To evaluate the other efficacy of 400 units of the product | <ul style="list-style-type: none"> • Changes in Numeric Rating Scale (NRS) for pain from baseline • Changes in other items of DAS from baseline • Clinical Global Impression of Change (CGI) of functional disability by a investigator • CGI of functional disability by a patient • Time to patient-reported onset of spasticity symptom relief • Patient-reported benefit of injection • Time to qualification for retreatment |
| To evaluate neutralizing antibody production | <ul style="list-style-type: none"> • Testing for neutralizing antibody |

5. STUDY DESIGN

5.1. Overall Design

This study is a 48-week multicenter, phase III study (a placebo controlled, randomized, double-blind comparative study and an open-label, uncontrolled study) to evaluate the efficacy and safety of the product in patients with post-stroke upper limb spasticity. The study period is up to 52 weeks, consisting of a screening phase up to 4 weeks, minimum 12-week blind phase (Part 1), maximum 36-week open-label phase (12 weeks per cycle with maximum 3 treatment periods, Part 2, Part 3 and Part 4). (Figure 5).

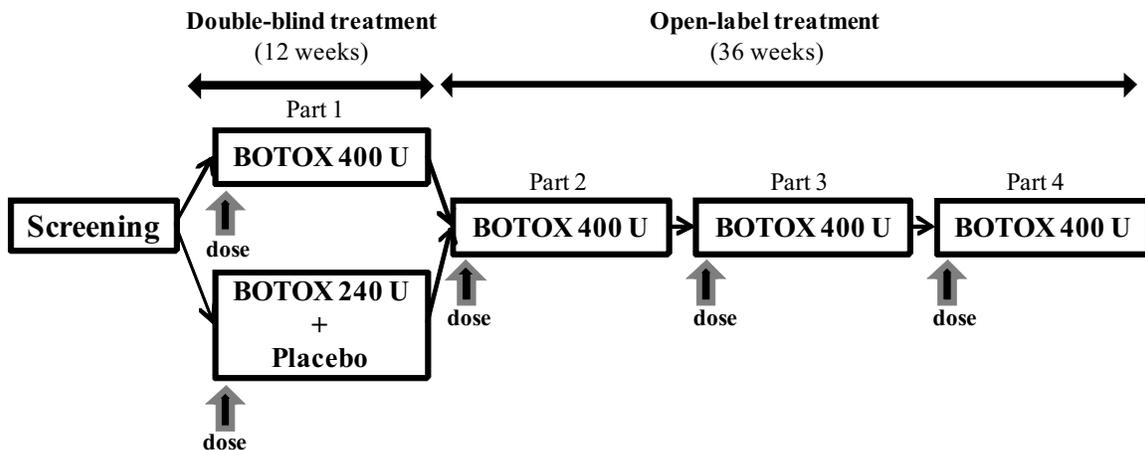


Figure 5 Study Design

In this study, the efficacy of 400 units of the product at Week 6 is evaluated, comparing to that of 240 units, and improvement tendencies are also evaluated in patients with post-stroke upper limb spasticity. The improvement will be defined as at least 1 reduction on the MAS score from baseline (a measurement value before injection of Day 1). The responder rate (the rate of the subjects that MAS score is reduced at least 1 from baseline) in the elbow flexors at Week 6 is set as an endpoint. As a point estimate, if the responder rate in the 400 units group outweighs that in the 240 units group, improvements tendencies will be considered to be positive.

For injection, use of the following any one of the tools: EMG, electrical stimulator, or ultrasonography, is recommended to ensure identification of the exact injection site. In the blind phase, use of at least one of the following tools: EMG, electrical stimulator, or ultrasonography, will be essential to ensure identification of the muscle to be injected correctly.

5.1.1. Screening Phase (up to 4 weeks)

Evaluation and screening tests will be performed 28 days to 7 days (+3 days) before initial injection (Day 1) as a starting point. The investigator will decide which arm to be injected during screening phase. Throughout the study period, the arm, which is decided to be injected at screening phase will be involved during the injections and evaluations, unless clearly specified otherwise by the sponsor.

5.1.2. Blind Period (minimum 12 Weeks): Placebo Controlled, Randomized, Double Blind Design

Subjects who meet the inclusion criteria will be randomized 1:1 to either the 400 units or the 240 units group.

- In the 400 units group, a total of 240 units of the product will be injected into the muscles that act on the finger (including thumb flexors) and wrist flexors, and a total of 160 units into the muscles that act on the elbow flexors; a total of 400 units of the product will be injected.
- In the 240 units group, a total of 240 units of the product will be injected into the muscles that act on the finger (including thumb flexors) and wrist flexors. Placebo will be injected into the muscles that act on the elbow flexors. A total of 240 units of the product will be injected.

If the total dose for the muscles that act on the finger and wrists flexors is ensured by 240 units, and 160 units for the muscles that act on the elbow flexors, the dose can be adjusted at an investigator's discretion based on the subject's symptoms. (Refer to "7.1. Treatments Administered" Table 2).

5.1.3. Open-Label Phase (maximum 36 weeks): Uncontrolled, Open-Label Design

The product of 400 units will be injected in both groups. The product can be injected up to 3 times after completion of Part 1 in the blind phase. In the open-label phase, subjects whom the investigator considers eligible for the injection will be treated (Refer to 5.1.3.1. Eligibility Criteria for Injection in and after Part 2). The next injection cannot be performed until the eligibility of the subject has been confirmed by the investigator (Refer to 5.1.3.1. Eligibility Criteria for Injection in and after Part 2).

In the open-label phase, the muscle to be injected and the dose will be decided by the investigator based on the patient's symptoms, and a total dose of 400 units of the product will be injected in a divided dose (Refer to "7.1. Treatments Administered" on Table 3). For the muscles that the investigator considers unnecessary to be treated, an injection may be skipped. The involving muscle and the dose do not have to be the same each time always.

5.1.3.1. Eligibility Criteria for Injection in and after Part 2

In the open-label phase (Part 2, Part 3, and Part 4), the subjects whom the investigator considers eligible for the injections in the open-label phase only will be treated. The eligibility is evaluated at a study visit after Week 12 (V5, if a subject does not meet the eligibility criteria, the evaluation will be performed at QRV (Qualification for Retreatment Visit). A subject will be considered as eligible when he or she meets all the criteria. The eligibility evaluation will be performed after completion of Part 1 in the blind phase, between Week 12 to Week 36. If a subject does not meet the eligibility at Week 36, subsequent evaluation will not be performed, and the product cannot be given (refer to Figure 1, Figure 2, Figure 3, and Figure 4).

- At least 12 weeks (84 days) have passed since the preceding dose
- Among the finger, wrist or elbow flexors, 2 flexors have at least 2 on the MAS (except only the finger and wrist flexors of 2 on the MAS)
- Subject who request the injection
- Subjects whom a investigator considers an injection of 400 units of the product is appropriate
- Subjects who were considered to remain freedom from unacceptable safety concerns (including potential for serious adverse events, laboratory data, electrocardiogram or pulmonary function test value) due to the injection of 400 units of the product
- Subjects who have not experienced serious adverse events (SAE) associated with the injection of the product

If a subject meets the criteria above at V5 or QRV, before injection of V1, the following items will be confirmed:

- Subjects with ≥ 40 kg in body weight
- Women of childbearing potential who have negative pregnancy test results in urine

5.2. Number of Participants

Approximately 120 subjects (approximately 60 in each group) will be randomized to obtain an evaluable subject sample of approximately 100 at Week 48 as subjects who complete the study

5.3. Participant and Study Completion

Subjects who completed all the study procedures, including a completion visit will be regarded as study completion. The completion date in this study will be defined as the last day performing the study procedure of last subject.

5.4. Scientific Rationale for Study

The study design was set to evaluate the efficacy and safety of 400 units of the product in patients with post-stroke upper limb spasticity. The primary endpoints employed the responder rate of the MAS score in the elbow flexors. The reasons for employing MAS score as an indicator include that MAS is highly reliable for evaluation of upper limb spasticity ([Bohannon, 1987](#); [Mutlu, 2008](#)); especially, for evaluation of spasticity in the elbow flexors in the upper limbs ([Gregson, 2000](#); [Sloan, 1992](#)).

Screening Phase

The screening phase up to 28 days before initial injection was set in order to confirm subjects meet the inclusion criteria and none of the exclusion criteria, and assess the condition of subjects at baseline. However, measurements of laboratory parameters at screening phase should be completed by 4 days before Day 1 (Day -28 to -4).

Treatment Phase

In Part 1, a double blind comparative study was set to compare the efficacy of the product of 400 units to 240 units, the currently approved dose for upper limb spasticity. In the blind phase, 240 units of the product will be injected into the muscles that act on the finger (including the thumb)/wrist flexors, and 160 units (the 400 units group) or placebo (the 240 units group) for the muscles that act on the elbow flexors. The improvement tendencies in the efficacy between the 240 units group, the total dose, and the 400 units groups will be compared by evaluating the responder rate tendencies on the MAS score in the elbow flexors in a blinded manner. In the previous confirmatory study (108509 study) for approval of the product for upper limb spasticity, the elbow flexors were not involved. Therefore, in this study, the responder rate on the MAS score in the elbow flexors was decided to compare as the placebo group.

Actually, in medical institutions, the product is injected into the whole upper limb, including the shoulder flexors. In addition, the dose for each muscle is decided at a investigator's discretion. Previous studies reported that botulinum injections into the pectoralis major and teres major muscle relieved pain in patients with hemiplegia (Marciniak, 2012) and injections into the sub-scapula improved passive range of motion (Yelnik, 2007). Therefore, in and after Part 2 in the open-label phase, the product will be allowed to be injected not only into the muscles that acts to the finger (including the thumb), wrist, and elbow flexors, but also the muscles that act on the shoulder flexors, where applicable, enabling a investigator to decide the dose for each muscle. In addition, the study design included safety evaluation of the product at Week 48 after initial injection in all subjects as far as possible for safety evaluation purposes of 400 units.

5.5. Dose Justification

The product of 400 units is a maximum dose for upper limb spasticity, which was approved by the U.S. Food and Drug Administration (FDA), and this suggests that the efficacy and safety profiles are favourable. Evaluation of the efficacy and safety of 400 units of the product provides beneficial information in Japanese patients with severe post-stroke upper limb spasticity, who are considered injections of 400 units of the product are necessary.

The dose of 240 units of the product, the controlled group, in the blind phase (Part 1) is the current authorized dose (a maximum dose per administration) for upper limb spasticity in Japan. In this study, the 240 units group was set as the control group in order to evaluate improvement tendencies, comparing the efficacy of 240 units of the product, the current approved dose, to that of 400 units of the product.

6. STUDY POPULATION

Inclusion of subjects despite expectation of deviation from the protocol, namely, exemption or discharge from the protocol, cannot be allowed.

6.1. Inclusion Criteria

6.1.1. Screening Phase (Day -28 to Day -1)

In the screening phase, subjects eligible for enrolment in the study must meet all of the following criteria. Laboratory parameters should be measured by 7 days (± 3 days) before initial injection (Day 1).

Age

1. Between 20 and 80 years of age at the time of informed consent (ICF).

Subjects and Characteristics of the Disease

2. Patients with at least a 3-month history of upper limb spasticity after the most recent stroke
3. Patients who have spastic symptoms in the finger (including the thumb), wrist, and elbow flexors whom the investigator considers the injections of 400 units of the product is necessary for the upper limb based on the muscle spasms and the symptoms of the patient
4. Patients who have a previous treatment history of 240 units of the product for the upper limb at least 16 weeks before screening (refer to [Table 3](#) for muscles in the upper limbs)
5. Patients who meet following criteria on MAS at screening (Test position : sitting)
 - At least 3 in for the elbow flexors
And
 - At least 2 in the finger or wrist flexors
6. Patients who have severe upper limb spasticity, which deserves to be treated with 400 units of the product in the divided dose and was previously injected 240 units of the product
7. Patients whom the investigator considers that enrolment in the study poses no problems based on the laboratory data results at screening
8. Patients who are free from a history of acute decreased lung function (hospitalization with aggravated asthma/COPD, pneumonia, or signs of pneumonia, or abnormal reactive airway diseases suggested on X-rays) within the last 3 months at screening and have stable pulmonary function

Body Weight

9. Body weight \geq 40 kg at screening

Sex

10. Male or female

a. Male Subjects

Male subjects must content to use highly effective contraceptive methods, which are shown on attachment 5 of the protocol in detail during the study period, and sperm donation must be avoided.

b. Female Subjects

Female subjects who are not pregnant or lactating are considered eligible (refer to attachment 5) if at least one of the following criteria is met:

- i) Non-childbearing potential based on the definition on attachment 5
- ii) Women of childbearing potential who content to follow the guidance about contraception on attachment 5 during the study period and at least for 3 months after the last dose of the product.
- iii) No plan of pregnancy during the study period

Informed Consent

11. Patients who have ability to sign their name on the ICF, following the description on attachment 3, adhering to the requirements and limitations described on the ICF and the protocol.

6.1.2. Day 1 (prior to injection)

Subjects eligible for enrolment in the study must meet all of the following criteria on Day 1 (prior to injection):

Subjects and Characteristics of the Disease

31. Patients who meet the following criteria on MAS score: (Test position : sitting)

- At least 3 in the elbow flexors
And
- At least 2 in the finger or wrist flexors

Preceding Treatments and Concomitant Medications/Therapies

32. If centrally acting muscle relaxants, tetracycline antibiotics, anticholinergics, benzodiazepines, or benzamides are given, the dose and regimen must be stable at least for the last 2 months before Day 1; Patients who can maintain the same dosage and regimens at least in the blind phase after initial injection (dose reductions and discontinuation of the drugs are acceptable in the open-label phase. However, second dose increase, resumption, and or new treatment will not be performed).
33. If intrathecal baclofen is given, the dose and regimen must be stable at least for the last 1 month before Day 1; Patients who can maintain the same dosage and regimens at least in the blind phase after initial injection (intravenous bolus is not acceptable, dose reductions and discontinuation of the drugs are acceptable. However, second dose increase, resumption, and or new treatment will not be performed).
34. If antiepileptic agents are given, the dose and regimen must be stable at least for the 1 month before Day 1; Patients who can maintain the same dose and regimens at least in the blind phase after initial injection (dose reductions and discontinuation of the drugs are acceptable in the open-label phase. However, second dose increase, resumption, and new treatment will not be performed).
35. If a physical therapy, occupational therapy, or a static splint on the study involvement upper limbs is given, the frequency and treatment regimen must be stable at least for the last 3 weeks before Day 1; Patients who can maintain the same dose and regimens at least in blind phase (In the open-label phase, the frequency and treatment regimen can be changed depending on the condition of spasticity).

6.2. Exclusion Criteria

6.2.1. Screening Phase (Day -28 to Day -1)

A subject will be excluded from enrolment in this study if any of the following criteria apply in the screening phase. Measurements of laboratory parameters at screening must be completed 7 days (± 3 days) before initial injection (Day 1).

Medical Condition

1. Patients present with spasticity requiring treatment in the non-paralytic side of the upper limb
2. Patients who have fixed contracture* in the finger (upper limb), wrist, elbow or shoulder muscle, which will be involved in the study

(*Positive effects were not confirmed in the previous treatment with GSK1358820, and contracture is considered to be the main cause of limited range of motion in the joint.)

3. Patients who have medically significant capsulitis or subluxation in any one of the fingers (upper limb), wrist, elbow and shoulder, which will be involved in the study, or whom a investigator considers the complicated local signs of pain may affect the efficacy evaluation
4. Patient's upper limb spasticity is attributed to other than stroke (traumatic brain injury, spinal cord injury, multiple sclerosis, or cerebral palsy)
5. Patients who have a 2-fold higher alanine aminotransferase (ALT) level than the upper limit of normal (ULN)
6. Patients who have a 1.5-fold higher bilirubin than the ULN (If a bilirubin fractionation shows direct bilirubin < 35%, a 1.5-fold higher free bilirubin than the ULN is acceptable).
7. Patients whom the investigator considers presence of a current medical history of unstable liver diseases or biliary tract diseases (the condition will be defined by development of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice or hepatic cirrhosis)

Note:

- If a patient with stable chronic liver diseases (Gilbert's syndrome, silent gallstone, and stable chronic hepatitis B or hepatitis C [Namely, hepatitis B surface antigen: HBsAg or hepatitis C virus: HCV antibody shows positive at screening or within 3 months before initiation of the study treatment] are included) meets other inclusion criteria, the patient can be enrolled in the study.

8. Patients with QTc > 450 msec or QTc > 480 msec in patients with bundle branch block

Note:

- QT intervals corrected by the Bazett method (QTcB); QT intervals corrected by the Fridericia method (QTcF) and/or QT intervals corrected by other methods; interpretation by a machine or manual re-interpretation will be used.
- Prior to study initiation, the correction formula which is used for the subject's inclusion/exclusion/discontinuation criteria will be determined. Namely, several different correction formula cannot be used for calculation of QTc in each subject. In addition, the lowest QTc level cannot be used for enrolment or discontinuation of subjects of the study.

Preceding Treatments and Concomitant Medications/Therapies

9. Patients who use peripherally acting muscle relaxants (dantrolene sodium, suxamethonium chloride, pancuronium bromide, vecuronium bromide, rocuronium bromide, etc.) within 1 week of screening.
10. Patients who use antibiotic agents with neuromuscular junction inhibitory effects: Aminoglycoside antibiotic agents (streptomycin sulfate, kanamycin sulfate, gentamicin sulfate, neomycin sulfate, spectinomycin hydrochloride, etc.), polypeptides (polymyxin B sulfate), lincomycins (lincomycin hydrochloride, clindamycin), and enviomycin sulfate within 1 week of screening.
11. Patients who was diagnosed as having a malignant tumor, or have a history of a malignant tumor within the last 5 years (except completely resected basal cell carcinoma or planocellular carcinoma at least 12 weeks before screening)

Previous Experience of Participation in a Clinical Studies/Current Participation in another Ongoing Study

12. Patients who have participated in another study of an investigational product or other medical research (a clinical study of pharmacotherapy, non-pharmacotherapy, or interventional device) within 30 days before screening, or are currently participating in a study

Evaluation by Diagnosis

13. Patients who are concerned likely to have an increased risk for an underlying medical condition/neurological disease due to exposure of the product; patients who have myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or a serious disease and use of a concomitant drug which may inhibit neuromuscular function
14. Patients with antihuman immunodeficiency virus (HIV) antibody positive
15. Patients who previously experienced allergic reactions or hypersensitivity due to botulinum toxin type A, an additive agent of sodium chloride, or human serum albumin
16. Patients who were previously suspected to have neutralizing antibody production by an investigator during an injection of botulinum toxin type A
17. Patients who have a skin disease such as infection at the site to be injected
18. Patients who suffer from serious and unstable disease, which could pose problems for the safety of subjects and study procedure compliance

6.2.2. Day 1 (Prior to injection)

A subject will be excluded from enrolment in this study if any of the following criteria apply on Day 1 (prior to injection):

Medical condition

31. Patients who placed a surgical cast or a dynamic splint within 3 months before Day 1 study visit, and/or these interventions are planned to be placed on the upper limb to be involved in the study

Preceding Treatments and Concomitant Medications/Therapies

32. Patients who were treated with botulinum toxin for spasticity of upper limb less than 16 weeks before Day 1 visit
33. Patients who underwent surgical interventions, phenol block, ethanol block or Muscle Afferent Block (MAB) within 12 months before Day 1 visit, or these interventions are planned during the study period in any one of the finger (upper limb), wrist, elbow or shoulder muscles, which will be involved in the study
34. Patients who have aspiration pneumonia, relapse of lower respiratory tract infection, uncontrollable asthma, uncontrollable COPD, and/or underlying or a history of serious respiratory dysfunction, which were clinically considered to be respiratory function impairment by an investigator within 12 months before Day 1 visit
35. Patients who have a history of aspiration, or an underlying and/or a history of the symptoms that suggests high risks for aspiration by an investigator within 12 months before Day 1 (serious salivation requiring changing in a type of diet, chronic dysphagia that is difficult to swallow)

36. Patients who were injected corticosteroid or an anesthetic agent into the finger (upper limb), wrist, or shoulder flexors, which will be involved in the study within 3 months before Day 1 visit, or these injections are planned during the study
37. Patients who received CIMT (constraint-induced movement therapy) within 3 months before Day 1 visit or CIMT is planned during the study
38. Patients who underwent ultrasound therapy, TENS (transcutaneous electrical nerve stimulation), electrical stimulation therapy, or acupuncture therapy in the upper arm, which will be involved in the study within 1 month before Day 1 visit, or these therapies are planned during the study

6.3. Lifestyle Restrictions

No limitations are required.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently [randomized/entered in the study]. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Rescreening

If a patient does not meet the participation criteria in the study (dropout during screening), the patient may undergo second screening only 1 time. If a patient does not meet following items, contact the medical monitor of the sponsor and gain his/her consent because validity of rescreening in subjects who dropped out needs to be judged carefully in the light of medical aspects.

- Subjects who did not meet the inclusion criteria for MAS (Inclusion criteria 5 at screening) and dropped out (However, the dropout period will be for within only 1 month from the dropout).
- For some reasons, a subject cannot make a study visit or undergo examination
- Sample collection or examination cannot be performed because of procedural or technical problems

The investigator must carefully consider the ethical aspects of subjects, and if other treatments are considered to give more treatment benefits for a subject, rescreening must not be conducted.

The rescreened subjects will be allocated a different subject identification number as upon initial screening.

7. TREATMENTS

Study treatment product is defined as any investigational treatment(s), and placebo to administer to a study participant according to the protocol.

7.1. Treatments Administered

| | | | |
|---|--|-----------|---|
| Study Treatment Name: | GSK1358820 (Nonproprietary name: Botulinum toxin type A) | | Placebo |
| Dosage formulation: | Injection | | Injection |
| Ingredient and quantity (Per vial) | Botulinum toxin A 100 units Sodium chloride 0.9 mg Human serum albumin 0.5 mg | | Sodium chloride 0.9 mg |
| Packaging and Labeling | It will be listed on the labelling in accordance with the regulatory requirements in Japan. | | It will be listed on the labelling in accordance with the regulatory requirements in Japan. |
| Manufacturer | Allergan (Ireland) | | Allergan (Ireland) |
| Dose | 400 units | 240 units | Dose |
| Dosing instructions | <p>Part 1: 240 or 400 units of the product will be injected into the muscles that act on the finger (including thumb flexors), wrist and elbow flexors, in accordance with Table 2. In and after Part 2: 400 units of the product will be injected into the muscles that act on the finger (including thumb flexors), wrist, elbow and shoulder flexors in accordance with Table 3. For the muscles that the investigator considers unnecessary to be treated, an injection may be skipped. Dose intervals should be at least 12 weeks.</p> <p>For adjustment of the product, the product will be dissolved with 2 ml of normal saline per 1 vial (100 units). The details will be described on Table 4.</p> | | |

In the blind phase

- A total of 240 units of product will be injected into the muscles that act on finger (including thumb flexors) and wrist flexors, and a total of 160 units of the product or placebo for the muscles that act on the elbow flexors in divided doses in accordance with [Table 2](#).
- The muscles which are not listed on [Table 2](#) must not be used.
- All of the muscles described on [Table 2](#) must be used. If the subject with no symptoms with thumb, the investigator does not have to inject to thumb.
- If the total dose for the muscles that act on the finger and wrists flexors is ensured by 240 units, and 160 units for the muscles that act on the elbow flexors, the dose can be adjusted at an investigator's discretion based on the symptoms of a subject.

In the open-label phase

- The investigator will decide the dose and the muscle to be injected based on the symptoms of patients, and a total of 400 units will be injected in divided doses. For the muscles that the investigator considers unnecessary to be treated, an injection may be skipped.
- The muscles to be injected must be chosen from [Table 3](#), and the muscles which are not listed on [Table 3](#) must not be used. For dose and number of injection site (sites/muscles), refer to [Table 3](#) and will be decided by investigator.

Table 2 Muscle Involvement and Dose in the Blind Phase

| Number | Muscles | The 400 units group Dose (units) | The 240 units group Dose (units) | Number of injection site (site and muscles) ³ | Joint |
|--------|--------------------------------|-------------------------------------|-------------------------------------|--|----------|
| A1 | Biceps brachii | 70 ¹ | Placebo | 2 | A.Elbow |
| A2 | Brachialis | 45 ¹ | | 1 | |
| A3 | Brachioradialis | 45 ¹ | | 1 | |
| B1 | Flexor carpi radialis | 50 ² | 50 ² | 1 | B.Wrist |
| B2 | Flexor carpi ulnaris | 50 ² | 50 ² | 1 | |
| C1 | Flexor digitorum profundus | 50 ² | 50 ² | 1 | C.Finger |
| C2 | Flexor digitorum superficialis | 50 ² | 50 ² | 1 | |
| D1 | Flexor pollicis longus | 20 ² | 20 ² | 1 | D.Thumb |
| D2 | Adductor pollicis | 20 ² | 20 ² | 1 | |
| | Total | 400 ² | 240 ² | 1 | - |

1: Within the limits of the total of 160 units (the elbow flexors), the dose will be decided by a investigator depending on the patient's symptoms.

2: Within the limits of the total of 240 units (the finger and wrist flexors), the dose will be decided by a investigator depending on the patient's symptoms.

3: When the dose exceeds 50 U per muscle, take into account the divided-injection.

Table 3 Muscle Involvement and Reference Dose in the Open-Label Phase
(Modified partially of "Dosing, Administration, and a Treatment Algorithm for Use of Botulinum Toxin A for Adult-Onset Spasticity.[Brin, 1997]")

| Number | Muscles ¹ | Dose (units) ² | Number of injection site (Sites/muscles) ² | Joint |
|--------|--------------------------------|---------------------------|---|------------|
| A1 | Biceps brachii | 50-200 | 4 | A.Elbow |
| A2 | Brachialis | 25-75 | 2 | |
| A3 | Brachioradialis | 25-75 | 2 | |
| B1 | Flexor carpi radialis | 25-100 | 2 | B.Wrist |
| B2 | Flexor carpi ulnaris | 10-50 | 2 | |
| C1 | Flexor digitorum profundus | 25-100 | 2 | C.Finger |
| C2 | Flexor digitorum superficialis | 25-75 | 4 | |
| C3 | Lumbricales interossei | 10-50/hand | 3 | |
| D1 | Flexor pollicis longus | 5-25 | 1 | D.Thumb |
| D2 | Adductor pollicis | 5-25 | 1 | |
| D3 | Opponens | 5-25 | 1 | |
| E1 | Pronator teres | 25-75 | 1 | E.Forearms |
| E2 | Pronator quadratus | 10-50 | 1 | |
| F1 | Teres major | 25-75 | 1 | F.Shoulder |
| F2 | Latissimus dorsi | 50-150 | 4 | |
| F3 | Pectoralis major | 75-150 | 4 | |
| F4 | Subscapularis | 25-75 | 1 | |

(Brin MF and the Spasticity Study Group, 1997)

1: The muscles which are not listed on Table 3 must not be used

2: For dose and number of injection site (sites/muscles), refer to Table 3 and will be decided by investigator.

Table 4 Muscle Involvement and Reference Dose in the Open-Label Phase

| Dose (units) | Injection Volume (ml) |
|--------------|-----------------------|
| 100 | 2.0 |
| 95 | 1.9 |
| 90 | 1.8 |
| 85 | 1.7 |
| 80 | 1.6 |
| 75 | 1.5 |
| 70 | 1.4 |
| 65 | 1.3 |
| 60 | 1.2 |
| 55 | 1.1 |
| 50 | 1.0 |
| 45 | 0.9 |
| 40 | 0.8 |
| 35 | 0.7 |
| 30 | 0.6 |
| 25 | 0.5 |
| 20 | 0.4 |
| 15 | 0.3 |
| 10 | 0.2 |
| 5 | 0.1 |

7.2. Dose Modification

Not applicable

7.3. Method of Treatment Assignment

After completion of all evaluations at screening phase/initiation of the blind phase, the subjects who met the inclusion criteria and none of the exclusion criteria will be given their randomization number at a case registry center and randomized to either the 240 or 400 units group. The assigned randomization number cannot be re-used. The table of the allocation will be prepared via a computer in GSK, using the RandAll systems.

Based on the MAS score (3 or 4) in the elbow flexors, subjects will be stratified at the time of randomization.

The subjects who meet the eligibility for the injections in the open-label phase can move forward to the open-label phase and be injected (Refer to section 5.1.3). In the open-label phase, 400 units of the product will be given to all subjects. Other detailed information will be described on SRM.

7.4. Blinding

This study consists of the blind phase (Part 1), followed by the open-label phase (Part 2 and subsequent Parts), and in the blind phase, following processes are applied.

A Role of the Person Responsible for Investigational Product Assignment

The person who is responsible for investigational product assignment will prepare an operating procedure for the assignment. The operation will be conducted in accordance with the operating procedure. The person who is responsible for the investigational product assignment will display the drug number on a container of the investigational product (investigational product and control drug)

after checking of the investigational product (investigational product and control drug) and the indistinguishability of packaging appearance. The confirmation of the investigational product (investigational product and control drug) and the indistinguishability of packaging appearance will be also performed after completion of the study. In addition, an operating procedure for occasion where the emergency treatment disclosure is required will be prepared. In response to the request of disclosure, unblinding procedures are performed for the requested drug only.

The unblinded subjects by the investigator will discontinue participation in the study. In addition, the major reasons for discontinuation (the event(s) or condition led to unblinding) will be described on case report form (CRF).

The Global Clinical Safety and Pharmacovigilance (GCSP) of the sponsor may disclose the assigned treatment in the subject, who experienced serious adverse events. For serious adverse events requiring emergency report to the regulatory authority, a copy of an emergency report on the assigned treatment of the subject may be sent to the study involving investigator in accordance with the regulations, policy of the sponsor, or both.

7.5. Preparation/Handling/Storage/Control

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual

7.6. Treatment Compliance

Subjects will be intramuscularly injected the product at a medical institution. The injection will be recorded in the source documents, and described in the case report form.

7.7. Concomitant Therapies

The medications that are used by subjects at the time of enrolment in the study or all medications and vaccines to be used during the study (over the counter drugs or prescribed drugs, vitamins, and/or herbal supplements) must be recoded with the following items:

- Reasons for use
- Initial date of administration and administration dates, including completion day
- Regarding the dose, including dosage and number of administration

Contact the medical monitor if there are any questions about concomitant therapies or preceding drugs.

7.7.1. Permitted Concomitant Drugs/Therapies

Following drugs and therapies are permissible only if a subject is already using them before initiation of the study. However, the dosage and administration will not be changed from the screening through completion of the blind phase. In and after open-label phase, dose reduction and discontinuation of the drugs will be allowed. However, once dose is decreased, re-increase will not be performed. If the drug(s) is/are discontinued, the drugs cannot be resumed. No new treatment will not be started after screening phase.

Rehabilitation therapies such as physical therapy, occupational therapy, and static splint are permissible. However, in the blind phase, the frequency and regimens (description of the therapy and intensiveness) for the upper limb, which involves in the study will not be changed. In addition, in the open-label phase, changing rehabilitation therapy to another one that seems to be the most appropriate for a subject is permissible based on the degree of improvements in spasticity. In such cases, the information will be described on CRF. Rehabilitation therapy will not be given on the day of investigational product injection.

- Central muscle relaxants
(baclofen, tizanidine hydrochloride, tolperisone hydrochloride, eperisone hydrochloride, chlorphenesin carbamate, afloqualone, etc.)
- Tetracycline antibiotics
(tetracycline hydrochloride, doxycycline hydrochloride, minocycline hydrochloride, etc.)
- Anticholinergics
(butylscopolammonium bromide, trihexyphenidyl hydrochloride, etc.)
- Benzodiazepines
(diazepam, etizolam, etc.)
- Benzamides
(tiapride hydrochloride, sulpiride, etc.)
- Antiepileptic drugs
(phenytoin, etc.)
- Intrathecal baclofen therapy

7.7.2. Contraindicated Medications/Therapies

Following drugs and therapies will be prohibited to use from screening phase through completion of the study:

- Botulinum toxin preparations
- Peripherally acting muscle relaxants
- (dantrolene sodium, suxamethonium chloride, pancuronium bromide, vecuronium bromide, rocuronium bromide)
- Antibiotic agents with neuromuscular junction blocking effects
 - Aminoglycosides
(streptomycin sulfate, kanamycin sulfate, gentamicin sulfate, neomycin sulfate, spectinomycin hydrochloride, etc.)

- Polypeptides
(polymyxin B sulfate)
- Lincomycins
(lincomycin hydrochloride, clindamycin)
- Enviomycin sulfate
- Nerve blocks such as phenol block, ethanol block and MAB for the upper limb
- Surgical cast or a dynamic splint
- A surgery for the upper limb (s)

Following drugs and therapies will be prohibited to use from screening phase through completion of the blinded-phase:

- CIMT (constraint-induced movement therapy)

7.8. Treatments after Completion of the Study

The investigator will take responsibility for subject's medical care after completion of the study, whether the sponsor provides a certain treatment or not.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

The efficacy of the investigational product used in this study sustains for about 3 to 4 months following a single dose, and thus daily dosage is not required; accordingly, treatment discontinuation shall not be defined in this study, and will be considered to be identical to subject withdrawal from this study.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- A subject discontinuing this study must visit the study site for study termination assessment promptly upon decision to discontinue the study.
- Refer to the schedule of assessment (SoA), completion visit (FV), for the details of data to be collected at the study discontinuation, and additional assessment that must be completed.

8.2.1. Liver Chemistry Stopping Criteria

A set of criteria for **study discontinuation and follow-up investigation based on hepatic function test** (in reference to FDA premarketing clinical liver safety guidance) is specified herein to ensure the safety of subjects and to evaluate the causes of hepatic events. The guidelines related to this protocol

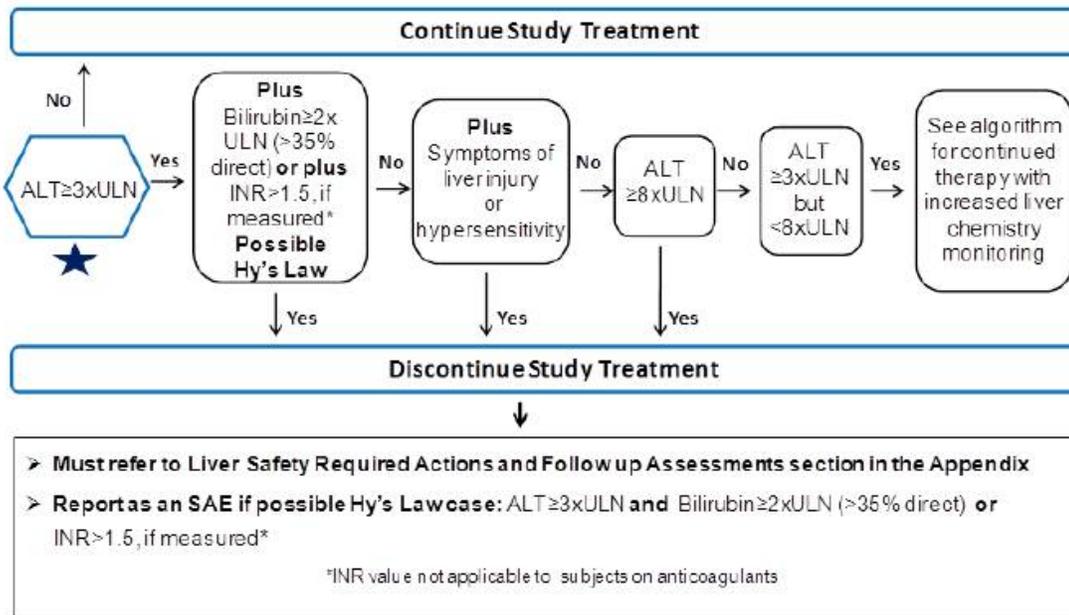
are based on the FDA premarketing clinical liver safety guidance:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>.

The investigator should consider discontinuing the study treatment upon discovery of liver function test abnormal, and if the subject is applicable to any of the symptoms presented in the algorithm, or such discontinuation is determined to be the best choice for the subject as judged by the investigator.

Algorithm A: Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm

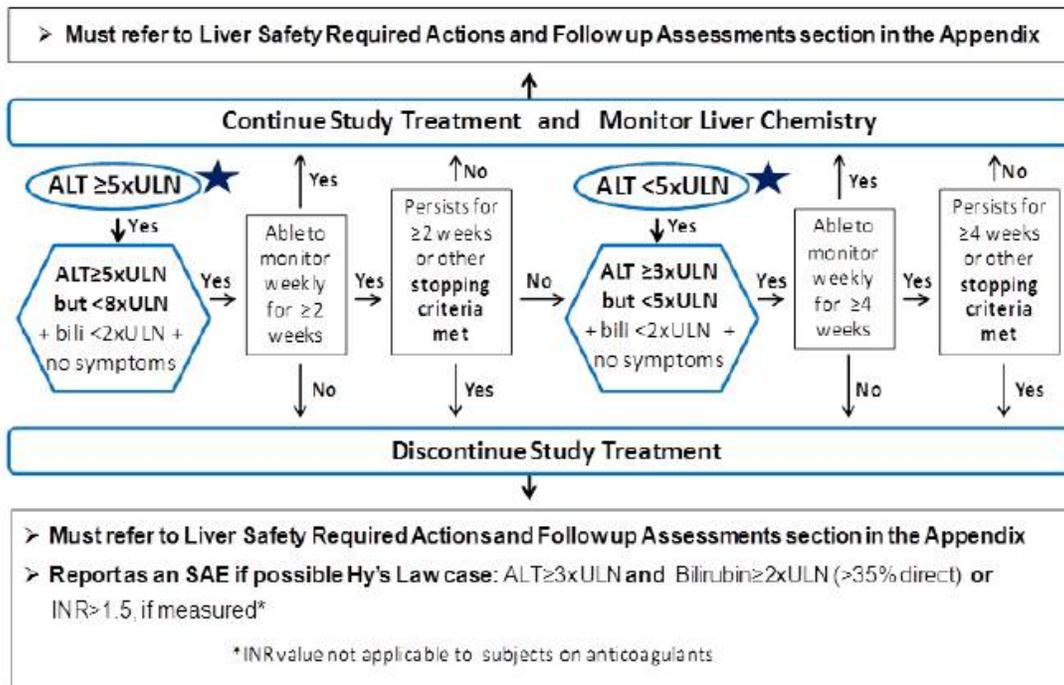
Algorithm A: Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

Algorithm B: Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT $\geq 3xULN$ but $< 8xULN$

Algorithm B: Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT $\geq 3xULN$ but $< 8xULN$



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

8.2.2. QTc Stopping Criteria

- For a decision on a subject's eligibility or study discontinuation, the same method for correction of QT interval must be used in the subject throughout the study, and must not be changed once the subject is enrolled.
 - For instance, if a subject is enrolled based on QTcB, decisions on the subject's withdrawal must be made based on QTcB.
 - The method used for correction of QT interval pertinent to the enrollment of a subject must be used for all QTc data to be collected throughout the study for the data analysis on the subject; provided that such rule is not applicable to ECG intended to ensure safety and also ECG not defined in the protocol.
- QTc should be determined based on a single measurement of ECG or the mean of ECG measured at 3 timepoints in a short period of time (e.g., 5 to 10 minutes). If abnormality is detected in a single measurement, ECG should be measured again, this time, at 3 timepoints.
- The lowest value of QTc cannot be used for a decision to withdraw a subject.

Refer to the schedule of assessment (SoA), completion visit (FV), for the details of data to be collected at the discontinuation of study treatment. Discontinue this study if the mean ECG is applicable to any of the following conditions:

- QTc >500 msec or uncorrected QT >600 msec
- Change in QTc from baseline >60 msec

The following withdrawal criteria should be applied for subjects with bundle branch block:

| Baseline for subjects with bundle branch block | Withdrawal criteria for subjects with bundle branch block |
|---|--|
| <450 msec | >500 msec |
| 450 to 480msec | IJYO530 msec |

8.2.3. Treatment discontinuation due to treatment-related SAE

A subject should be withdrawn from this study if treatment-related serious adverse event has occurred.

8.2.4. Treatment discontinuation due to pregnancy

A female subject who become pregnant during this study must be withdrawn from the study.

8.2.5. Withdrawal of subjects who start receiving prohibited medications or therapies

If a prohibited medication or therapy (See section 7.7.2.) needs to be started during the study, the subject must be withdrawn from this study; in which case, the subject must make the study completion visit (FV) before starting the prohibited medication or therapy.

8.2.6. Prohibition of treatment resumption

Study treatment must not be resumed in subjects who are once withdrawn from this study for a reason associated with hepatic function test, QTc, treatment-related serious adverse event, pregnancy, or commencement of a prohibited medication or therapy.

8.3. Lost to follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.

9.1. Efficacy assessments

9.1.1. Evaluation methods

9.1.1.1. Modified Ashworth Scale (MAS)

According to "2. SCHEDULE OF ACTIVITIES (SoA)" the investigator will use MAS (Table 5) to evaluate the level of spasticity. MAS should be measured and evaluated by the investigator, physiotherapist, or occupational therapist who has been given the training as an assessor.

The test should be performed on sitting position throughout the study. The affected parts should be extended as fast as possible to grade the flexor muscle tones. The final assessment will be made by the investigator in consideration of the information from physiotherapist or occupational therapist. The assessor should in principle remain unchanged throughout the study period.

Table 5 Modified Ashworth Scale (MAS)

| | |
|----|---|
| 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 ROM (range of movement) |
| 2 | More marked increase in muscle tone through most of the ROM, 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 measurement as inclusion criteria (Screening and Day 1)

The subject's wrist or fingers and elbow should all be evaluated as inclusion criteria. Subjects meeting the eligibility and randomized should be evaluated for MAS at Visit 1 of Treatment Period 1 on the same day; provided that measurement may be performed only once if the affected part to be evaluated is the same. The detail of inclusion criteria are shown in 6.1.

- MAS measurement during the blinded period

The subject's wrist, fingers and thumb should all be evaluated during the blinded period. Likewise, the subject's wrist, fingers and thumb should all be evaluated for MAS at Visit 5 and QRV of the blinded period. Subjects meeting the eligibility and transferred to the open-label period should be evaluated for MAS at Visit 1 of Treatment Period 2 on the same day; provided that measurement may be performed only once if the affected part to be evaluated is the same. Meanwhile, MAS needs to be evaluated again if the affected part to be evaluated is not the same.

- MAS measurement during the open-label period

During the open-label period, MAS should be evaluated for the flexors at which the muscle given the study treatment functions (fingers, thumb, wrist, elbow, fore-arm) (Table 6). If the subject is determined to be eligible, the V5/QRV and V1 would be on the same day, and therefore, the MAS measured at V5/QRV of the previous treatment period should not be measured again on V1; the measurement on V5/QRV should be used for the assessment (Figure 6). MAS on flexors to be newly

assessed on V1 should be evaluated before dose on V1. The MAS on the shoulder should be evaluated comprehensively for the adductor and inverter.

Table 6 Regions to be evaluated for MAS during the open-label period

| Number | Muscles to be injected | Regions to be evaluated for MAS |
|--------|--------------------------------|--|
| A1 | Biceps brachii | Elbow flexors (flexion) |
| A2 | Brachialis | |
| A3 | Brachioradialis | |
| B1 | Flexor carpi radialis | Wrist flexors (flexion) |
| B2 | Flexor carpi ulnaris | |
| C1 | Flexor digitorum profundus | Fingers (flexion) |
| C2 | Flexor digitorum superficialis | |
| C3 | Lumbricales interossei | |
| D1 | Flexor pollicis longus | Thumb (flexion, adduction and opposition) |
| D2 | Adductor pollicis | |
| D3 | Opponens pollicis | |
| E1 | Pronator teres | Forearm (pronate) |
| E2 | Pronator quadratus | |
| F1 | Teres major | Shoulder (adduction and internal rotation) |
| F2 | Latissimus dorsi | |
| F3 | Pectoralis major | |
| F4 | Subscapularis | |

| Visit | SV | Part 1 | | | | | Part 2 | | | | | Part 3 | | | | | Part 4 | | | | | |
|------------|----|--------|----|----|----|----|--------|----|----|----|----|--------|----|----|----|----|--------|-----|----|----|----|---|
| | | V1 | V2 | V3 | V4 | V5 | V1 | V2 | V3 | V4 | V5 | V1 | V2 | V3 | V4 | V5 | V1 | V2 | V3 | V4 | V5 | |
| A.Elbow | ● | ● | ● | ● | ● | ● | (○) | ● | ● | ● | ● | (○) | ● | ● | ● | ● | (○) | ● | ● | ● | ● | ● |
| B.Wrist | ● | ● | ● | ● | ● | ● | | | | | | | ● | ● | ● | ● | ● | (○) | ● | ● | ● | ● |
| C.Finger | ● | ● | ● | ● | ● | ● | (○) | ● | ● | ● | ● | (○) | ● | ● | ● | ● | (○) | ● | ● | ● | ● | ● |
| D.Thumb | | ● | ● | ● | ● | ● | | | | | | | | | | | | | | | | |
| E.Forearm | | | | | | | ● | ● | ● | ● | ● | (○) | ● | ● | ● | ● | (○) | ● | ● | ● | ● | ● |
| F.Shoulder | | | | | | | ● | ● | ● | ● | ● | | | | | | ● | ● | ● | ● | ● | |

● : MAS measurement (before treatment)
 (○) : Use V5 or QRV MAS measurement

Figure 6 Subjects to be evaluated for MAS

9.1.1.2. Numeric Rating Scale (NRS)

According to "2. SCHEDULE OF ACTIVITIES (SoA)" the investigator (or subinvestigator) will use NRS (Figure 7) to evaluate the severity of flexors pain.

The investigator will perform the interview on NRS following the assessment of MAS. Each subject will be interviewed on the severity of pain on the treated part when extended based on a scale with 0 being "no pain" and 10 being "the worst imaginable pain"; 1 response on the scale should be selected by the subject.

| | | | | | | | | | | |
|---------|---|---|---|---|---|---|---|---|---|--------------------------------|
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| No pain | | | | | | | | | | Pain as bad as you can imagine |

Figure 7 Numeric Rating Scale (NRS) for pain

- NRS measurement during the blinded period

During the blinded period, the severity of pain in the elbow flexors will be evaluated.

- NRS measurement during the open-label period

During the open-label period, a major part with pain [specify 1 part from among fingers, thumb, wrist, elbow, fore-arm (pronate), and shoulder] will be evaluated for the severity of pain on Visit 1. The part to be evaluated does not have to be the same within each treatment period, but should be the same part as that evaluated for MAS.

9.1.1.3. Disability Assessment Scale (DAS)

According to "2. SCHEDULE OF ACTIVITIES (SoA)" the investigator (or subinvestigator) will use the 4 disability assessment parameters presented in Table 7 and evaluate all of them based on the scale presented in Table 8. Before starting the study treatment, the investigator shall discuss with the subject, and select and evaluate 1 parameter agreed with the subject as the "main assessment parameter." The assessor should in principle remain unchanged throughout the study period. The main assessment parameter should also remain unchanged throughout the study period.

Table 7 Disability assessment parameters

| | Content of assessment |
|--------------|--|
| Hygiene | The extent of maceration/ulceration and/or palmar infection, palm/hand cleanliness, ease of cleanliness, ease of nail trimming, and interference with hygiene-related disability in the subject's daily life |
| Pain | The intensity of pain/discomfort, and the interference that upper-limb pain-related disability has in the patient's daily life. |
| Dressing | The difficulty or ease for the subject in putting on the relevant clothing (e.g., shirts, jackets, gloves, etc.) and the interference that upper-limb dressing-related disability has in the patient's daily life. |
| Limb posture | The psychological and/or social interference that the disfigured upper limb has in the patient's daily life. |

Table 8 Disability Assessment Scale

| | Description |
|-----------------------------|--|
| 0: No functional disability | No functional disability |
| 1: Mild disability | Noticeable but does not interfere significantly with normal activities |
| 2: Moderate disability | Normal activities require increased effort and/or assistance. |
| 3: Severe disability | Normal activities limited. |

9.1.1.4. Clinical Global Impression of Change (CGI) assessed by a investigator

The investigator (or subinvestigator) will evaluate CGI according to "2. [SCHEDULE OF ACTIVITIES \(SoA\)](#)"; Changes in spasticity (Clinical Global Impression) from baseline (before dose on Day 1) will be evaluated by 9 grades as shown in [Table 9](#).

The investigator shall also consider the subject's clinical symptoms and adverse events pertinent to the assessment of CGI. Also, the therapeutic effect of the product injected in the subject's fingers, wrist, and elbow should be taken into an account. The assessor should in principle remain unchanged throughout the study period.

Table 9 Clinical Global Impression of Change (CGI)

| | |
|----|---------------------|
| -4 | Very much worsened |
| -3 | Much worsened |
| -2 | Moderately worsened |
| -1 | Slightly worsened |
| 0 | Unchanged |
| +1 | Slightly improved |
| +2 | Moderately improved |
| +3 | Much improved |
| +4 | Very much improved |

9.1.1.5. Clinical Global Impression of Change (CGI) assessed by a patient

According to "2. [SCHEDULE OF ACTIVITIES \(SoA\)](#)" the investigator (or subinvestigator) will use [Table 9](#) to record subject-reported CGI. The investigator shall interview each subject on changes in spasticity from predose, and the subject will evaluate it using [Table 9](#).

9.1.1.6. Time to patient-reported onset of spasticity symptom relief (Visit 2):

According to "2. [SCHEDULE OF ACTIVITIES \(SoA\)](#)" the investigator (or subinvestigator) will record the time to alleviation of spasticity reported by subjects. The investigator shall ask the subject whether the product was effective on the spasticity, and if the subject's response to the question is positive, ask him/her "how many days did it take for the therapeutic effect to appear after the current dose?" and record the number of days.

9.1.1.1. Patient-reported benefit of injection (Visits 3, 4, and 5)

According to "2. [SCHEDULE OF ACTIVITIES \(SoA\)](#)" the investigator (or subinvestigator) will record the efficacy of treatment reported by subjects. The investigator shall ask, "Was the product effective?" and the subject shall respond either by "Yes" or "No."

9.2. Adverse events

Definitions of adverse events and serious adverse events (SAE) are as specified in Appendix 4. The investigator or a person assigned by the investigator is responsible for detecting, recording, and reporting events that match the definitions of adverse events and SAEs, and also, responsible for follow-up investigations on SAEs, as well as events related to the study drug or this study, and events that resulted in treatment discontinuation or subject withdrawal (See section 8).

9.2.1. Period subject to collection of data related to adverse events and SAEs, and the frequency of such data collection

- All SAEs will be collected from the start of treatment until Final Visit at the time points specified in the SoA (Section 2).
- All AEs will be collected from the start of treatment until Final Visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4 . The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4 .

9.2.2. Method used to detect adverse events and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.2.3. Follow up on adverse events and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory requirements of SAE reporting

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Cardiovascular events and death

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

9.2.6. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study treatment and until Final Visit.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix [X].
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.3. Management of overdose

A dosage of the product exceeding 400 units within 24 hours shall be considered as overdose in this study. Overdose may cause excessive pharmacodynamic responses such as hyposthenia, muscular paralysis, and other localized adverse reactions. Symptoms and signs may not immediately appear following dose. Moreover, blepharoptosis, dysarthria, dysphagia, dyspnea, myasthenia, and other events suspected to be an effect on other muscles distal to the treated muscle have been reported overseas. If such a symptom appears, the subject should be carefully monitored, and given appropriate interventions, if necessary with hospitalization. Also, supportive therapies such as artificial breathing should be considered for respiratory symptoms.

Upon confirmation of overdose, the investigator should;

1. Contact the Medical Monitor immediately.

Carefully monitor the adverse event/SAE, and laboratory abnormalities in the subject for at least 4 weeks; and

Document the quantity of the excess dose as well as the duration of the overdosing in the CRF..

The investigator shall discuss with the sponsor's medical monitor on the clinical assessment of the subject, and upon which, decide whether or not to discontinue the study treatment.

9.4. Safety assessments

Assessment timepoints for all safety parameters are as shown in SoA.

9.4.1. Physical examination

Physical examination (complete version): Only during screening

- The head and neck, skin, lungs, cardiovascular system, abdominal region (liver and spleen), gastrointestinal system, lymph node, and nervous system should be examined, and the results thereof should be recorded; these organs should be examined for the presence/absence of pre-existing conditions and abnormal findings, and if there is any suspected abnormality, detailed examinations should be performed.
- The pulmonary function test should be conducted in details if any sign of pulmonary impairment is found. For the pulmonary function test, spirometry by pulmonologists is recommended.

Physical examination (simplified version): To be conducted only if an eligibility criterion is not met during the open-label period.

- At least, the lungs, cardiovascular system, and abdominal region (liver and spleen) should be examined, and the results thereof should be recorded.
- The investigator should pay attention to clinical signs and symptoms related to a history of serious disease.

The physical examinations should be performed by doctors in accordance with the standard clinical guidelines of each study site.

9.4.2. Vital signs

- For the vital signs, body temperatures (oral, intra-aural, or axillary fossa), systolic/diastolic blood pressures, and pulse rates should be measured in a semi-recumbent position after a 5-minute rest.
- If a temperature is to be measured orally, the subject must refrain from eating food or drinking beverage within 5 minutes before the measurement. The method for the measurement of body temperature must remain the same throughout the study.
- The blood pressures and pulse rates should be measured with an automated device. A manual method may be used only if there is no automated device available for use.

9.4.3. Height and weight

The standard clinical guidelines of each study site should be followed.

9.4.4. ECG

- QTc should be determined based on a single measurement of ECG or the mean of ECG measured at 3 timepoints in a short period of time (e.g., 5 to 10 minutes).

- An automated measurement in accordance with SoA should be used to collect data on the heart rates, PR, QRS, QT, and QTc interval. Refer to section 8.2.2. for QTc-related treatment discontinuation standard, and additional QTc to be measured as required.
- Each interval between timepoints for the measurement of ECG should be minimized as much possible (within 2 minutes). The measurement of ECG should be performed 3 times consecutively and completed within 5 to 10 minutes.

9.4.5. Neutralizing antibody test

The investigator shall draw blood for neutralizing antibody samples in accordance with the study schedule. The neutralizing antibody will be measured collectively by a central laboratories designated by GSK (Intertek Pharmaceutical Services Co. and Pacific BioLabs Co.). The screening samples will be retained temporarily by the central laboratories, and then, upon retrieval of samples from all subjects, will be collected and tested by Intertek for screening. Samples tested positive at Intertek will be separately sent to Pacific BioLabs for retest to finalize the results of neutralizing antibody test. The above procedures shall also be taken for samples collected for Week 12 visit during the blinded period, and upon completion of study treatment in all subjects.

9.4.6. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory parameters that should be tested, and to SoA for the timepoints and frequency of testing.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If a result of clinical laboratory test not scheduled in the protocol is obtained by a study site, which requires a change in the patient management, or is determined to be clinically important by the investigator, that is SAE, adverse event, an event requiring dose modification, or any other relevant event, the record thereof must be documented in the CRF.
- Follow-up investigation may be performed at any time during the study as determined to be necessary by the investigator, or required by the Japanese regulation.

9.5. Pharmacokinetics

PK parameters are not evaluated in this study.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics/Pharmacogenetics

Genetics and pharmacogenetics are not evaluated in this study.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

9.9. Pharmacoeconomics

Pharmacoeconomic parameters are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

This study is not intended to verify a statistical hypothesis, but is rather intended to verify that the responder rate in the 400 units group exceeds that in the 240 units group, and for which, about 120 subjects (60 in each treatment group) are to be enrolled.

During Treatment Period 1 of this study, 160 units of the product will be administered in the muscle which affects the elbow; thus, the sample size was determined in reference to an overseas phase III study (Study 127) in which a similar dosage as this study (150 units) was administered in the muscle which affects the elbow. The responder rate in the elbow at Week 6 of the initial dose in Study 127 was 72.2% and 47.1% in the product 300 units group (150 units in the muscle which affects the elbow flexors) and placebo group, respectively. The number of subjects in the intention-to-treat (ITT) population was small in both the product 300 units group and placebo group of Study 127, which was 18 subjects each; thus, considering the uncertainty of the results of Study 127, the responder rates in the product 400 units and 240 units groups in this study were conservatively assumed to be 70.0% and 50.0%, respectively. Assuming that the sample size is 60 subjects in each group, the power of test to detect an intergroup difference in the responder rates would be about 62% with a two-sided significance level of 5% while the probability of the responder rate in the product 400 units group to exceed that in the product 240 units group as a point-estimate would be $\geq 98\%$.

With about 120 subjects enrolled, 100 subjects are expected to complete Week 48 of the initial dose.

10.2. Populations for Analyses

Populations for statistical analyses in this study are defined as follows.

| Population | Description |
|------------|--|
| ITT | All subjects randomized in the study and had at least 1 post-baseline efficacy assessment: ITT is the primary efficacy analysis population, and the subjects will be analyzed in line with the randomized treatment group. |
| Safety | All subjects randomized in the study and received study treatment at least once: The subjects will be analyzed based on the treatment actually given. |

10.3. Statistical Analyses

10.3.1. Efficacy Analyses

This study is not intended to verify a statistical hypothesis; thus, there will be no statistical test.

All of the efficacy analyses will be performed on the ITT population separately for the blinded period and the open-label period.

| Endpoints | Statistical Analysis Methods |
|-------------|---|
| Primary | <p>The primary endpoint is the proportion of subjects whose MAS score on the elbow at Week 6 of the initial dose decreased by at least 1 level from the baseline (responder rate). The primary endpoint will be calculated as the proportion of subjects whose MAS score decreased by at least 1 level from the baseline in the ITT population. Also, a 95% confidence interval of the intergroup difference in the responder rate will be computed. Subjects with no MAS score available at Week 6 will not be counted as subjects whose MAS score decreased by at least 1 level from the baseline (that is, counted in as non-responder).</p> <p>The MAS scores, 0, 1, 1+, 2, 3, and 4 will be encoded to 0, 1, 2, 3, 4, and 5, respectively, for the analysis purpose.</p> |
| Secondary | <p>Unless specified otherwise, the data up to Week 12 of treatment will be summarized for each repeated dose during the open-label period.</p> <p>During the blinded period, a mixed model for repeated measurement (MMRM) will be used for the analysis on the endpoints specified below, and the least-square mean and 95% confidence interval will be calculated. The details of the model will be described in the statistical analysis plan. For the open-label period, only a summary statistics will be performed for each treatment group. Missing values will not be imputed.</p> <ul style="list-style-type: none"> · Change in MAS score in the fingers, thumb, wrist, and elbow from the baseline · Change in Disability Assessment Scale (primary endpoint) from the baseline <p>The proportion of subjects in whom MAS score in the fingers, thumb, wrist, and elbow decreased by at least 1 level from the baseline (responder rate) during the blinded period will be analyzed with the same method as that for the primary endpoint. For the open-label period, the denominator to be used for the calculation of responder rate shall be the number of subjects in each subgroup stratified by the number of injections given, not the ITT population. Also, a 95% confidence interval of the intergroup difference in the responder rate will not be calculated.</p> |
| Exploratory | <p>Time to patient-reported onset of spasticity symptom relief will be evaluated for subjects who reported alleviation of spasticity at in 2 weeks postdose. The number of days from dose to the alleviation of spasticity will be summarized for each treatment group.</p> <p>Clinical Global Impression of Change (CGI) assessed by a investigator, CGI assessed by a patient, and Patient-reported benefit of injection will be summarized for each treatment group. Missing values will not be complemented.</p> <p>Other details will be specified in the statistical analysis plan.</p> |

10.3.2. Safety Analysis

Safety analyses will all be performed on the safety population separately for the blinded and open-label periods.

| Endpoints | Statistical Analysis Method |
|-------------|--|
| Primary | Not applicable |
| Secondary | Adverse events that occurred in the overall study period, blinded period, and open-label period will be summarized for each treatment group. For the blinded period, 2 patterns of analyses on adverse events will be performed; one is on adverse events that occurred between the initial dose and the first dose in the open-label period (or at the completion of study if no dose is given in the open-label period or at the study withdrawal), and another one is on adverse events that occurred within 84 days from the initial dose. Adverse events will be summarized separately for SOC (system organ class) and PT (preferred term). Also, adverse events related to study treatment, adverse events that resulted indiscontinuation, adverse events by subgroups stratified by severity, and serious adverse events will be summarized. Laboratory findings and vital signs at each visit and their changes from baseline will be summarized for each treatment group. |
| Exploratory | Will be specified in the statistical analysis plan. |

10.3.3. Other analyses

Other analyses will be specified in the statistical analysis plan.

10.3.4. Interim analyses

The details of the interim analysis plan will be specified in the statistical analysis plan.

When all subjects (except for early termination) complete the visit at Week 24 of the initial dose, the data on all of the subjects until Week 24 of the initial dose may be locked, unblinded, and analyzed for reporting to authorities.

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12. Appendices

12.1. Appendix 1: Abbreviations and trademarks

Trademark

| Trademark of Glaxo Smithcline Group | Trademarks that do not belong to Glaxo Smithcline Group |
|-------------------------------------|---|
| Botox | — |

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in [Table 10](#) will be performed by central laboratory.
- A test needs to be performed by study sites only if the result cannot be obtained from the central laboratory in time for study treatment and/or assessment. Even if measurement is performed at a study site, another sample at the same assessment timepoint is separately required for measurement at central laboratory. If a result of measurement at the study site is to be used for a decision of study treatment and/or assessment, the result should be recorded in the CRF.
- Protocol-specific inclusion/exclusion criteria are as specified in section 6 of the protocol.
- Protocol-specific inclusion/exclusion criteria are as specified in section 6 of the protocol.

Table 10 Protocol-Required Safety Laboratory Assessments

| Clinical laboratory | Parameters | | | |
|--|--|-----------------------------------|--|---|
| Hematological tests | Platelet count | Erythrocyte indices: | | Percentage of white blood cell: Neutrophil Lymphocyte Monocyte Eosinophil Basophil |
| | RBC | Mean corpuscular volume (MCV) | | |
| | Hemoglobin | Mean corpuscular hemoglobin (MCH) | | |
| | Hematocrit | Reticulocyte count (%) | | |
| | White blood cell count | | | |
| Chemistry ¹ | Urea nitrogen (BUN) | Potassium | Aspartate aminotransferase (AST) / Serum glutamic oxaloacetic transaminase (SGOT) ¹ | Total bilirubin and direct bilirubin |
| | Creatinine | Sodium | Alanine aminotransferase (ALT) / Serum glutamic pyruvic transaminase (SGPT) ¹ | Total protein |
| | Calcium | Alkaline phosphatase | | |
| Urinalysis | Specific gravity PH with test paper, glucose, protein, occult blood, ketone, bilirubin, urobilinogen, nitrite, and white blood cell esterase Microscopy (if occult blood or protein is deviated) | | | |
| Other tests | <ul style="list-style-type: none"> Pregnancy test (if necessary in a woman of child-bearing potential): Serum or urine human chorionic gonadotropin (hCG)² <p>The following parameters should be tested during the screening period.</p> <ul style="list-style-type: none"> Serological verification: HIV antibody The following parameters should be tested only for subjects with chronic hepatitis B or C that is stabilized at screening, and subjects currently receiving or expected to receive immunosuppressant. <ul style="list-style-type: none"> Serological verification: Hepatitis B virus surface antigen (HBsAg), and hepatitis C virus antibody The following parameter should be tested for women of no child-bearing potential. <ul style="list-style-type: none"> Follicle stimulating hormone and estradiol | | | |
| Caution: 1. Details of the discontinuation criteria based on hepatic function test, and the interventions and follow up necessary after the occurrence of hepatic events are specified in section 8.1 and Appendix 6. SAEs must be reported for all events with ALT IJYO3 times the upper limit of normal range (ULN), and at the same time, bilirubin IJYO2 times the ULN (direct bilirubin >35%), or ALT IJYO3 times the ULN, and at the same time, the international normalized ratio (INR) >1.5 if measured [which suggests a possibility of severe liver injury (applicable to Hy's Law)]. 2. Pregnancy tests should be performed with serum samples at screening, and with urine samples for routine tests after randomization. | | | | |

12.3. APPENDIX 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
 - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
 - Applicable ICH Good Clinical Practice (GCP) Guidelines
 - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
 - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
 - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
 - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Process of obtaining consent

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Data protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Composition of committee

No committee will be established.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- Disclosure of a Clinical Study Report (CSR) after the evaluation by the regulatory authority(ies).
- GSK may post the study information and tabulated-form study results on the website (www.ClinTrials.gov) of the U.S. National Institution of Health (NIH) or other websites open to the public
- GSK may post the study results to scientific journals that conduct peer review in order to report the study results.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the corresponding list of source documents.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.4. APPENDIX 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of an SAE

If an event does not correspond any of the above definitions of an AE, even if it is a serious condition, it will not be regarded as an SAE (e.g.; hospitalization due to the signs/symptoms of the disease being studied, death caused by exacerbation of the disease).

A SAE is defined as any untoward medical occurrence that, at any dose:**a. results in death****b. is life-threatening**

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. requires hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the investigator's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. is congenital anomaly/birth defect

f. other important medical situations:

- Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/angina unstable
- Cardiac failure congestive
- Arrhythmia
- Valvular disease
- Pulmonary hypertension
- Cerebrovascular event/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep vein thrombosis/pulmonary embolism
- Revascularisation

Recording of AEs and SAEs**AE and SAE Recording**

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and classify it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities - An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as “serious”, not when it is assessed as severe but when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of causality

- The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE.
- A “reasonable possibility” is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgement to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated.
- The investigator will also consult the IB, for marketed products, in the determination of his/her assessment.
- The investigator **must** record that he or she reviewed AEs and SAEs and assessed the causality in the medical record.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, prepare and send the follow-up report of SAE by amending the assessment result of the causality accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit all updated SAE data to GSK within 24 hours after obtaining the information.

Reporting of SAEs to GSK**SAE Reporting to GSK via Electronic Data Collection Tool**

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the SAE coordinator by telephone.
- Contacts for SAE reporting can be found in ATTACHMENT.

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE page of the CRF is the preferred method to transmit the information on SAEs to GSK.
- In rare circumstances and in the absence of facsimile equipment, initial notification by telephone is acceptable followed by a copy of the SAE page of the CRF sent by overnight mail or by courier.
- Initial notification via the telephone does not replace the need for the investigator (or subinvestigator) to complete and sign the SAE page of the CRF within the designated reporting time frames.
- The ATTACHMENT 1 shows a contact information to which the SAEs should be reported.

12.5. APPENDIX 5: Contraceptive Guidance and Collection of Pregnancy Information

Definition

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP

1. Premenarchal

Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

Postmenopausal women

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male study subject

- A male study subject who has a female partner of childbearing potential can participate in this study if he agrees to any of the following conditions:
- He must agree not to have a sex (sexual intercourse) with a person of the opposite sex as a normal favourable lifestyle (continuously having no sex for a long period of time) and also agree to keep that condition.
- If he has a sex with a woman of childbearing potential, he must agree to use a male condom and use at least one of the contraception methods with an annual failure rate below 1% which are shown in Table 11.
- A male study subject who has a pregnant or breastfeeding female partner must agree not to have a sex from the time during the study or use a male condom when having a sex.
- A male study subject must agree not to provide his sperm during the study.

Female study subject

A female study subject of childbearing potential can participate in this study if she agrees to use any of the extremely effective methods of contraception shown in Table 11 continuously and accurately. Among the methods of contraception shown in Table 11, those deleted with strikethrough lines have neither been approved nor been accepted in Japan.

Table 11 Extremely effective methods of contraception

| |
|--|
| User-dependent extremely effective methods of contraception ^a Their annual failure rates are below 1% if they are used continuously and accurately. |
| Contraception by mixed (estrogen and progestogen-containing) hormone preparation (inhibit ovulation) ^b <ul style="list-style-type: none"> • Oral • Intravaginal • Transdermal |
| Contraception by only progestogen-containing hormone preparation (inhibit ovulation) ^b <ul style="list-style-type: none"> • Injection |
| User-independent extremely effective methods of contraception |
| <ul style="list-style-type: none"> • Contraception by only progestogen-containing implantable hormone preparation (inhibit ovulation)^b • Intrauterine device (IUD) • Intrauterine system (IUS) • Bilateral tubal occlusion |
| Male partner's vasectomy (If her male partner has been vasectomised, it is an extremely effective method of contraception for a woman of childbearing potential if that partner is the only man with whom she has a sex and it has been confirmed that he is sterile. Otherwise, he/she must use other additional extremely effective method(s) of contraception.) |
| Having no sexual relations (If the subjects decides to refrain himself or herself from having a sex of the opposite sex for the entire period when there is a risk of the investigational product, abstinence is deemed to be an extremely effective method of contraception. However, the credibility of abstinence needs to be evaluated during the study period and from the perspectives of the subject's normal favourable lifestyle.) |

Notes:

- a. The usual failure rate is different from the rate when contraception is used continuously and accurately. The subjects should use the methods of contraception that match with regulations concerning the methods of contraception for study subjects in each country.
- b. The efficacy of contraception by hormone preparations may decrease as a result of the interaction with the investigational product. In that case, the subject should use two extremely effective methods of contraception during the treatment period and at least for 3 months after the last dose of the investigational product.

Pregnancy test

- A woman of childbearing potential can be enrolled to this study only if it is confirmed that she is negative in a highly sensitive serum pregnancy test along with her menstrual period.
- Pregnancy test should be performed if no menstruation occurred or she is suspected to be pregnant.
- Analysis should be performed according to the package insert using a testing kit provided by GSK.

Collection of pregnancy information**If a male study subject's partner becomes pregnant**

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

For a female study subject who discovers her pregnancy while participating in this study,

- The administration of the investigational product will be discontinued.

12.6. APPENDIX 6: Liver Safety Required Actions and Follow up Assessments

In order to secure the subject's safety and evaluate the causes of liver event, **the criteria for discontinuation and follow-up based on the liver function test values in the phase III-IV studies** will be stipulated.

Criteria for discontinuation based on the liver function test values in the phase III-IV studies and necessary follow-up

| Criteria for discontinuation based on the liver function test values | |
|---|--|
| ALT | ALT \geq 8xULN |
| ALT increase | ALT \geq 5xULN but <8xULN persists for \geq 2 weeks ALT \geq 3xULN but <5xULN persists for \geq 4 weeks |
| Bilirubin ^{1,2} | ALT \geq 3xULN and bilirubin \geq 2xULN (>35% direct bilirubin) |
| INR ² | ALT \geq 3xULN and INR>1.5, if INR measured |
| Cannot Monitor | ALT \geq 5xULN but <8xULN and cannot be monitored weekly for \geq 2 weeks ALT \geq 3xULN but <5xULN and cannot be monitored weekly for \geq 4 weeks |
| Symptom ³ | ALT \geq 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity |
| Necessary measures and assessment items for liver event | |
| Actions | Follow Up Assessments |
| <ul style="list-style-type: none"> Immediately discontinue the administration of the investigational product. Report it to GSK within 24 hours. Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE². Perform liver event follow up assessments Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below) Do not restart/rechallenge participant with study treatment unless allowed per protocol and GSK Medical Governance approval is granted If the resumption/re-administration of the investigational product is not stipulated in the protocol or approved by GSK's Medical Governance, the administration of the investigational product will be discontinued | <ul style="list-style-type: none"> Viral hepatitis serology⁴ Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend Only in those with underlying chronic Hepatitis B at study entry (identified by positive Hepatitis B surface antigen) quantitative Hepatitis B DNA and Hepatitis delta antibody⁵ Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). Fractionate bilirubin, if total bilirubin \geq 2xULN Obtain complete blood count with differential to assess eosinophilia Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. |

| | |
|--|--|
| <p>permanently and the follow-up prescribed in the protocol 8.1. will be conducted.</p> <p>MONITORING: <u>For bilirubin or INR criteria:</u></p> <ul style="list-style-type: none"> Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline A specialist or hepatology consultation is recommended <p><u>For other criteria:</u></p> <ul style="list-style-type: none"> Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72 hrs Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline | <ul style="list-style-type: none"> Record alcohol use on the liver event alcohol intake case report form (CRF) page <p><u>For bilirubin or INR criteria:</u></p> <ul style="list-style-type: none"> Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms. |
|--|--|

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT $\geq 3xULN$ and bilirubin $\geq 2xULN$. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.

All events of ALT $\geq 3xULN$ and bilirubin $\geq 2xULN$ (>35% direct bilirubin) or ALT $\geq 3xULN$ and INR>1.5, if INR measured which may indicate severe liver injury (possible ‘Hy’s Law’), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)

Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen (HbsAg) and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody

Criteria for follow-up with continued treatment based on the liver function test values in the phase III-IV studies

| Criteria for follow-up based on liver test function values – Liver events to be followed | |
|---|---|
| Criteria | Actions |
| <p>ALT \geq5xULN and $<$8xULN and bilirubin $<$2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 2 weeks.</p> <p>OR</p> <p>ALT \geq3xULN and $<$5xULN and bilirubin $<$2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks.</p> | <ul style="list-style-type: none"> • Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT \geq5xULN and $<$8xULN to \geq3xULN but $<$5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT $<$3xULN and bilirubin $<$2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline. |

12.7. APPENDIX 7: COUNTRY SPECIFIC DESCRIPTIONS

12.7.1. Regulatory and Ethical Considerations

This study will be conducted in compliance with the “Good Clinical Practice (GCP)” (MHW Ordinance No. 28, March 27, 1997) and the “Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, etc. (PMD Act)”.

GSK will submit the CTN to the regulatory authorities in accordance with the PMD Act before concluding the study agreement with the medical institution

12.7.2. Obtaining of Informed Consent

Prior to participation in the study, the investigator should fully inform the potential subject and/or his or her legally acceptable representative of the study using the information document. In doing so, the investigator should provide the subject sufficient time and opportunity to inquire about details of the study and obtain the subject and/or his or her legally acceptable representative’s signature or printed name and seal and date of consent on the consent form. The subject may take the informed consent form home to review it. The person who provided the explanation and the clinical research coordinator who provided the supplementary explanation should also sign or affix his or her printed name and seal on the consent form and enter the date of signature. If an impartial witness is needed, he or she should also sign or affix his or her printed name and seal on the consent form and enter the date of witness. The investigator should attach the original of the above signed or affixed with printed name/seal and dated consent form (and information document) to the original medical record such as medical chart (in accordance with the rules for records retention, if any, at each medical institution), retain it, and give a copy to the subject and/or his or her legally acceptable representative.

12.7.3. Study Implementation Period

July 2017 – February 2019

12.7.4. Study Conduct Structure

The Attachment 1 shows the sponsor’s information. Also, the Attachment 2 shows a list of medical institutions and investigators.

TITLE PAGE

Protocol Title: A phase III study (a placebo controlled, randomized, double-blind comparative study and an open-label, uncontrolled study) to evaluate the efficacy and safety of GSK1358820 in patients with post-stroke upper limb spasticity

Protocol Number: 01

Short Title: A phase III study to evaluate the efficacy and safety of GSK1358820 in patients with post-stroke upper limb spasticity

Compound Number: GSK1358820

Sponsor

GlaxoSmithKline K.K. (GSK)

6-15, Sendagaya 4-chome, Shibuya-ku, Tokyo 151-8566 Japan

The person responsible for operation of the study: PPD Director of Development of Drugs for Neurological Diseases, Department of Development, Clinical Research Department

Medical Monitor Name and Contact Information are shown on SRM.

Regulatory Agency Identifying Number(s):NA

Approval Date: 24-MAY-2017

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Signature of the Sponsor:

PPD

Director of Development of Drugs For Neurological Diseases,
Department of Development, Clinical Research Department
GlaxoSmithKline K.K. (GSK)

Date

The IMMS document approved is as follows:

Unique ID :

System Version:

Effective Date:

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|-------------------|-------------|
| Document | Date |
| Amendment 1 | 24-MAY-2017 |
| Original protocol | 4-APR-2017 |

Amendment 1 : 24-MAY-2017

Overall Rationale for the Amendment:01

The protocol was changed based on the regulatory inquiries by the Pharmaceuticals and Medical Devices Agency (PMDA).

Overall Rationale for the Amendment:01

| Section # and Name | Description of Change | Brief Rationale |
|--|---|--|
| 1. SYNOPSIS | Add pulmonary test and description adjustment | Requested by PMDA |
| 2. SCHEDULE OF ACTIVITIES (SoA) | Add pulmonary test and description adjustment | Requested by PMDA |
| 5.1.3.1. Eligibility Criteria for Injection in and after Part 2 | Add pulmonary test | Requested by PMDA |
| 6.1.1. Screening Phase (Day -28 to Day -1) | Add pulmonary test | Requested by PMDA |
| 6.2.2. Day 1 (Prior to injection) | Description adjustment | Establish consistency with section 7.7.2 |
| 6.4. Screen Failures | Description adjustment | Not shown due to minor changes |
| 7.7.2. Contraindicated Medications/Therapies | Description adjustment | Establish consistency with section 6.2.2 |
| 9.1.1.4. Clinical Global Impression of Change (CGI) assessed by a investigator | Error correction | Not shown due to minor changes |
| 9.4.4. Pulmonary test | Add pulmonary test | Requested by PMDA |
| 9.4.5.ECG | Description adjustment | Add manual re-interpretation |

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1. SYNOPSIS

Protocol Title: A phase III study (a placebo controlled, randomized, double-blind comparative study and an open-label, uncontrolled study) to evaluate the efficacy and safety of GSK1358820 in patients with post-stroke upper limb spasticity

Short Title: A phase III study to evaluate the efficacy and safety of GSK1358820 in patients with post-stroke upper limb spasticity

Rationale:

GSK1358820, botulinum toxin type A (hereafter referred as the product), is sterile, purified type A botulinum neurotoxin complex. Intramuscularly injected botulinum neurotoxin shows muscle relaxant effects by blocking the neuromuscular junction and inhibiting release of acetylcholine, a neurotransmitter. Since the approval of the product for strabismus and blepharospasm in US in 1989, the product is licensed for the treatment of various diseases, which respond to the muscle relaxant effects in more than 90 countries (as of Apr 2017).

In Japan, the product is licensed with 8 indications as an ethical drug so far: blepharospasm as a first indication in Oct 1996, followed by “hemifacial spasm” in Jan 2000, “spasmodic torticollis” in Jun 2001, “talipes equinus associated with lower limb spasticity in pediatric patients two years of age and older with cerebral palsy” in Feb 2009, “upper limb spasticity” and “lower limb spasticity” in Oct 2010, “severe primary maschalephidrosis” in Nov 2012, and “strabismus” in Jun 2015. For “upper limb spasticity,” 240 units of the product is approved as a maximum dose per administration. In US, as a maximum dose per administration, 400 units of injection of the product have been approved for the treatment of upper limb spasticity in adult patients in 2015; therefore, the authorized dose of the product between US and Japan is different.

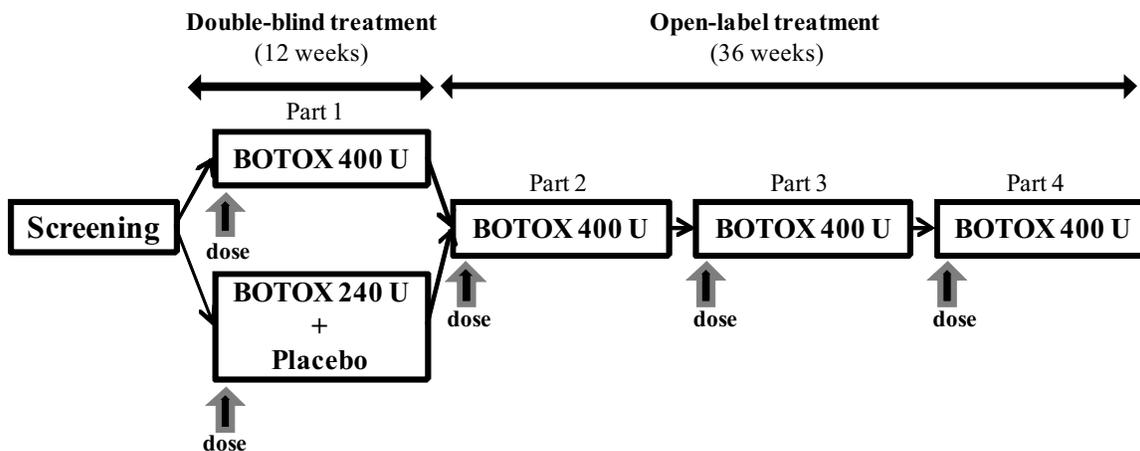
This study is a multicenter, double blind, placebo controlled phase III domestic study and aims to evaluate the efficacy and safety of 400 units of the product in patents with post-stroke upper limb spasticity. The study was planned to increase the maximum dose per administration in Japan to 400 units from 240 because the treatment with 240 units of the product, a maximum dose per administration, is considered to be insufficient in some patients with post-stroke upper limb spasticity.

Objectives and Endpoints:

| Objectives | Endpoint(s) |
|---|--|
| Primary | |
| To evaluate the efficacy of the injections of 400 units of the product at Week 6 (finger/ wrist flexors: 240 units, elbow flexors: 160 units), comparing to that of 240 units (finger/ wrist flexors: 240 units, elbow flexors: placebo). | The responder rate : The rate of the subjects that Modified Ashworth Scale (MAS) score was reduced at least 1 from baseline in the elbow flexors. |
| Secondary | |
| To evaluate the efficacy of 400 units of the product, comparing to 240 units of the product | <ul style="list-style-type: none"> • The responder rate of MAS score from baseline in the finger, thumb and wrist flexors • Changes in MAS score from baseline in the finger, thumb, wrist and elbow flexors • Changes in Disability Assessment Scale (DAS) from baseline |
| To evaluate the safety and tolerability of the product of 400 units, comparing to 240 units of the product/ To evaluate the safety and tolerability of 400 units of the product | <ul style="list-style-type: none"> • Adverse events • Physical examinations • Clinical laboratory tests (haematology, blood biochemistry, urinalysis) • Vital signs (heart rate, blood pressure, body temperature) |
| Exploratory | |
| To evaluate the efficacy of 400 units of the product | <ul style="list-style-type: none"> • Changes in MAS score from baseline in finger, thumb, wrist, elbow, pronation of the forearm and shoulder flexors |
| To evaluate the other efficacy of the product of 400 units, comparing to 240 units of the product/ To evaluate the other efficacy of 400 units of the product | <ul style="list-style-type: none"> • Changes in Numeric Rating Scale (NRS) for pain from baseline • Changes in other items of DAS from baseline • Clinical Global Impression of Change (CGI) of functional disability by a investigator • CGI of functional disability by a patient • Time to patient-reported onset of spasticity symptom relief • Patient-reported benefit of injection • Time to qualification for retreatment |
| To evaluate neutralizing antibody production | <ul style="list-style-type: none"> • Testing for neutralizing antibody |

Overall Design:

This study is a 48-week multicenter, phase III study (a placebo controlled, randomized, double-blind comparative study and an open-label, uncontrolled study) to evaluate the efficacy and safety of the product in patients with post-stroke upper limb spasticity. The study period is up to 52 weeks, consisting of a screening phase up to 4 weeks, minimum 12-week blind phase (Part 1), maximum 36-week open-label phase (12 weeks per cycle with maximum 3 treatment phases: Part 2, Part 3 and Part 4).

**Number of Participants:**

Approximately 120 subjects (approximately 60 in each group) will be randomized to obtain an evaluable subject sample of approximately 100 at Week 48 as subjects with completion of the study.

Treatment Groups and Duration:**Screening Phase (Day -28~Day -1)**

Evaluation and screening tests will be performed 28 to 7 days (± 3 days) before initial injection (Day 1) as a starting point. The investigator will decide which arm to be injected during screening phase.

Blind Phase (minimum 12 Weeks): Placebo Controlled, Randomized, Double Blind Design

Subjects who meet the inclusion criteria will be randomly assigned 1:1 to either the 400 or the 240 units group.

- In the 400 units group, a total of 240 units of the product will be injected into the muscles that act on the finger (including thumb flexors) and wrist flexors, and a total of 160 units into the muscles that act on the elbow flexors; a total of 400 units of the product will be injected.
- In the 240 units group, a total of 240 units of the product will be injected into the muscles that act on the finger (including thumb flexors) and wrist flexors. Placebo will be injected into the muscles that act on the elbow flexors. A total of 240 units of the product will be injected.

If the total dose for the muscles that act on the finger and wrists flexors is ensured by 240 units, and 160 units for the muscles that act on the elbow flexors, the dose can be adjusted at an investigator's discretion based on the subject's symptoms.

Open-Label Phase (maximum 36 Weeks): Uncontrolled, Open-Label Design

The product of 400 units will be injected in both groups. The product can be injected up to 3 times after completion of Part 1 in the blind phase. In the open-label phase, subjects whom the investigator considers eligible for the injections will be treated. The next injections cannot be performed until the eligibility of the subject has been confirmed by the investigator.

In the open-label phase, the muscle to be injected and the dose will be decided by the investigator based on the patient's symptoms, and a total dose of 400 units of the product will be injected in a divided dose. For the muscles that the investigator considers unnecessary to be treated, an injection may be skipped. The involving muscle and the dose do not have to be the same each time always.

Eligibility Criteria for Injection in and after Part 2

In the open-label phase (Part 2, Part 3, and Part 4), only the subjects whom the investigator considers eligible for the study will be injected. The eligibility is evaluated at a study visit after Week 12 (V5). If a subject does not meet the criteria at V5, the eligibility is evaluated at QRV (Qualification for Retreatment Visit). Subjects are considered to be eligible if following criteria are all satisfied:

- 1) At least 12 weeks (84 days) have passed since the preceding dose
- 2) Among the finger, wrist or elbow flexors, 2 flexors have at least 2 on the MAS (except only the finger and wrist flexors of 2 on the MAS)
- 3) Subject who request the injections
- 4) Subjects whom a investigator considers an injection of 400 units of the product is appropriate
- 5) Subjects who have not experienced serious adverse events (SAE) associated with the injections of the product

If subjects meet the criteria of the above 1) to 5) at V5 or QRV, body weight measurement, ECG, pulmonary function test, and pregnancy test will be performed to evaluate the following items. If subjects meet the following 6) to 8), the subjects will move forward to V1.

- 6) Body weight ≥ 40 kg
- 7) Subjects who the investigator considers there are no unacceptable safety concerns [potential for serious adverse events, laboratory data (V5), electrocardiogram (ECG) or pulmonary function value] due to 400 U of BOTOX
- 8) Woman of childbearing potential who have negative pregnancy test result in urine

Pulmonary function test must be performed at V5 even if subjects do not meet the above 1) to 5) in accordance with the study operation schedule (SoA).

2. SCHEDULE OF ACTIVITIES (SoA)

Compliance with the protocol (including the list of the study conduct schedule) is important and required to conduct the study. Therefore, exemption or discharge cannot be allowed, except but emergency safety concerns arise.

The study operation schedule is shown on [Table 1](#). Examples of injections in the open-label phase based on evaluation of eligibility for injection are shown on [Figure 1](#), [Figure 2](#), [Figure 3](#), and [Figure 4](#).

Table 1 SCHEDULE OF ACTIVITIES (SoA)

| Visit | Screening ^a SV | Blind phase If a subject meets the eligibility at V5/ QRV, the subject will move forward to the open-label phase | | | | | | Open-label phase If a subject meets the eligibility at V5/QRV, the subject will move forward to the next treatment phase | | | | | | Completion visit Final Visit |
|--|------------------------------|--|----|----|----|--|---|--|----|----|----|--|---|---------------------------------------|
| | | Part 1 | | | | | Eligibility evaluation ^b | Part 2/Part 3/ Part 4 | | | | | Eligibility evaluation ^b | |
| | | V1 (Day 1) | V2 | V3 | V4 | V5 ^c (Eligibility evaluation) | QRV | V1 | V2 | V3 | V4 | V5 ^d (Eligibility evaluation) | QRV | |
| Time from initial injection (Day 1) (Weeks) | — | 0 | 2 | 4 | 6 | 12 | Allowable Week 16 to 36 ^e | — | — | — | — | — | Allowable Week 24 to 36 ^e | 48/ Withdrawal |
| Time from injection day in each treatment phase (Weeks) | — | 0 | 2 | 4 | 6 | 12 | 16/ 20/ 24/ 28/ 32/ 36 | 0 | 2 | 4 | 6 | 12 | 16/ 20/ 24 | - |
| Acceptable visit windows (days) | — | ±4 | ±4 | ±4 | ±4 | +4 ^f | ±14 ^g | +4 | ±4 | ±4 | ±4 | +4 ^f | ±14 ^g | ±4 |
| Written informed consent | X ^h | | | | | | | | | | | | | |
| Randomization | | X ⁱ | | | | | | | | | | | | |
| Injections | | X | | | | | | X | | | | | | |
| Evaluation of eligibility | | | | | | X | X | | | | | X | X | |
| Inclusion/exclusion criteria ^j | X | X ⁱ | | | | | | | | | | | | |
| Subject demography | X | | | | | | | | | | | | | |
| MAS ^k | X | X ⁱ | X | X | X | X | X | X ^{l,t} | X | X | X | X | X | X |
| NRS ^l | | X ⁱ | X | X | X | X | X | X ^{l,t} | X | X | X | X | X | (X) ^r |
| DAS | | X ⁱ | X | X | X | X | X | X ^{l,t} | X | X | X | X | X | (X) ^r |
| CGI by a investigator | | | X | X | X | X | X | | X | X | X | X | X | (X) ^r |
| CGI by a patient | | | X | X | X | X | X | | X | X | X | X | X | (X) ^r |
| Time to patient-reported onset of spasticity symptom relief | | | X | | | | | | X | | | | | |
| Patient-reported benefit of injection | | | | X | X | X | X | | | X | X | X | X | (X) ^r |
| Physical examination (complete version) | X | | | | | | | | | | | | | |
| Physical examination (simplified version) | | X ⁱ | | | | X | | X ^{l,t} | | | | X | | X |
| Medical history | X | X ⁱ | | | | | | | | | | | | |
| Vital signs ^m | X | X ⁱ | | | | X | | X ^{l,t} | | | | X | | X |
| Height | X | | | | | | | | | | | | | |
| Body weight | X | | | | | X ^u | X ^u | | | | | X ^u | X ^u | |
| Pulmonary function test | X | X | | | | X | X ^u | | | | | X | X ^u | X |
| Electrocardiogram | X | | | | | X ^u | X ^u | | | | | X ^u | X ^u | |
| Pregnancy test ⁿ | X | X ⁱ | | | | X ^u | X ^u | | | | | X ^{s,u} | X ^u | X |
| Laboratory test ^o | X | | | | | X | | | | | | X | | X |
| Adverse events ^p | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications/therapies | X | X ⁱ | X | X | X | X | X | X | X | X | X | X | X | X |

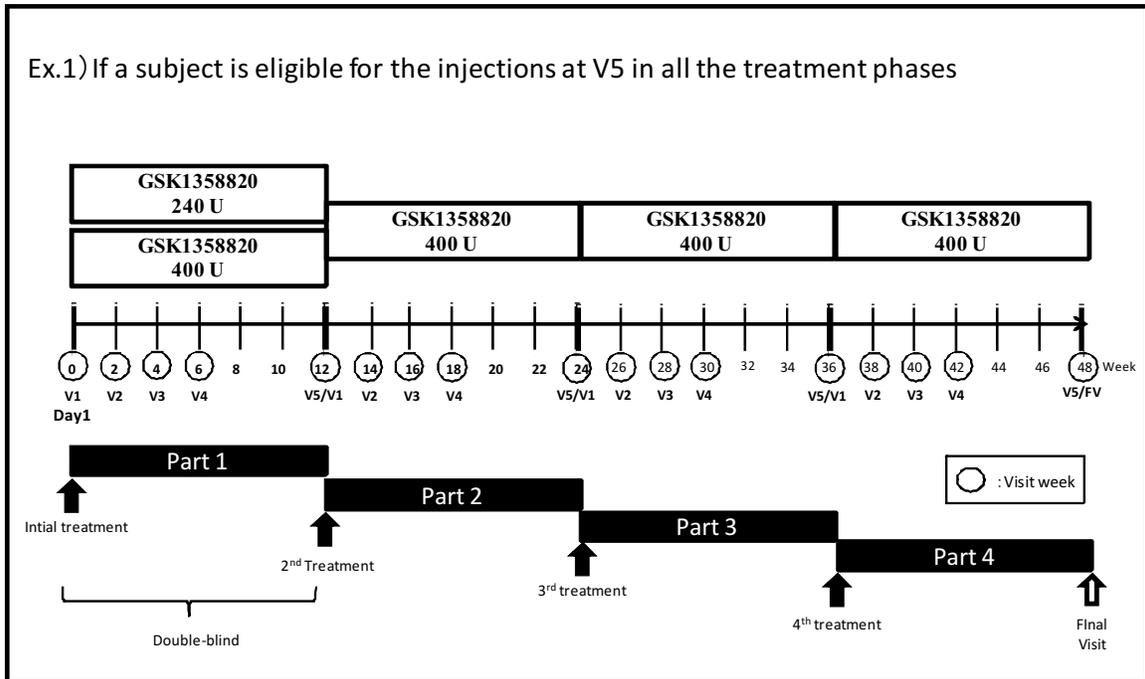


Figure 1 Eligibility Evaluation in the Open-Label Phase (Example 1)

If a subject is eligible for the injections at V5 in all the treatment phases, 4 injections will be performed throughout the study. Week 48 visit is performed also as a completion visit.

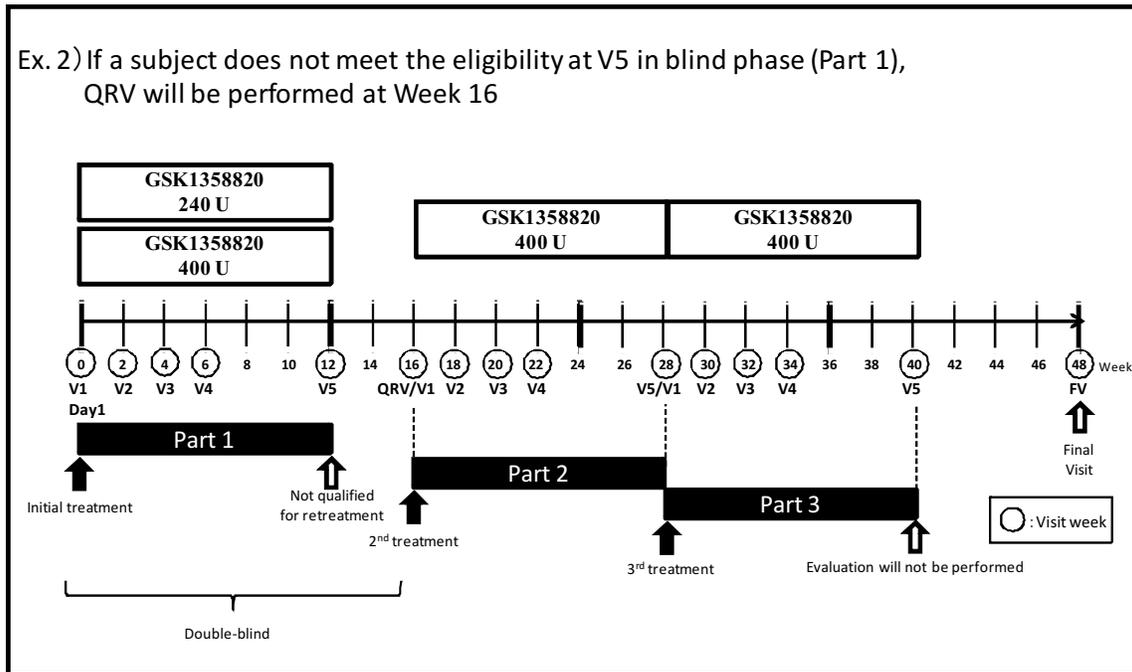


Figure 2 Eligibility Evaluation in the Open-Label Phase (Example 2)

If a subject does not meet the eligibility at V5 in blind phase (Part 1), QRV will be performed at Week 16. V5 in Part 3 is at Week 40, therefore, eligibility evaluation will not be performed. After V5 at Week 40, FV will be performed at Week 48.

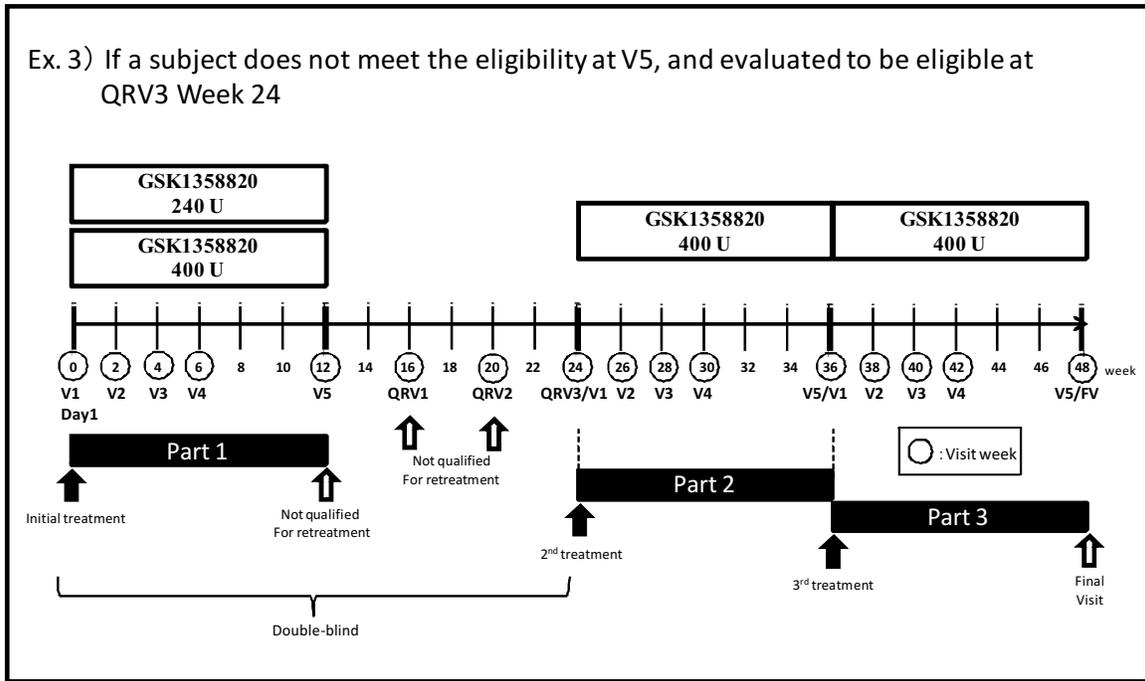


Figure 3 Eligibility Evaluation in the Open-Label Phase (Example 3)

If a subject does not meet the eligibility at V5 in the blind phase (Part 1), QRV will be performed until the eligibility have confirmed at 4 weeks intervals, at V5 as a starting point. If a subject is evaluated to be eligible at QRV3 Week 24, the injections in Part 2 will be performed on the same day as QRV3. V5 in Part 3 is in Week 48, therefore, at V5, completion visit (FV) will be also performed.

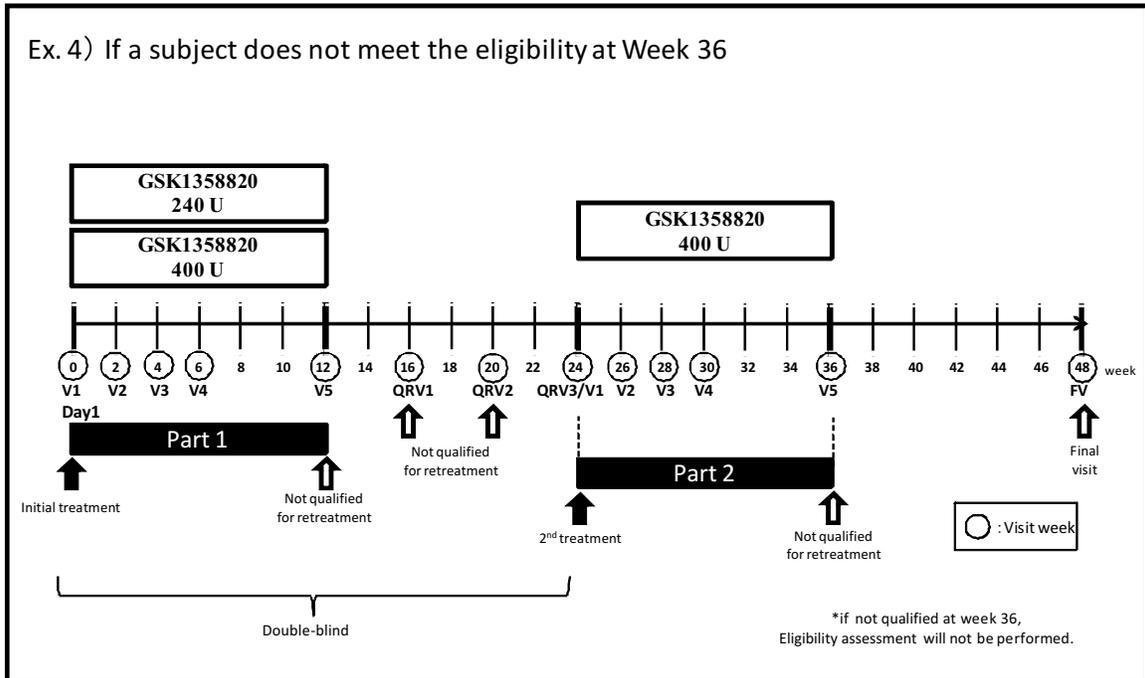


Figure 4 Eligibility Evaluation in the Open-Label Phase (Example 4)

QRV in Part 2 is Week 36, and if a subject does not meet the criteria, subsequent injections will not be performed, and Week 48 completion visit will be performed.

3. INTRODUCTION

3.1. Study Rationale

GSK1358820, botulinum toxin type A (hereafter referred to as the product) is sterile, purified type A botulinum neurotoxin complex. Intramuscularly injected botulinum neurotoxin shows muscle relaxant effects by blocking the neuromuscular junction and inhibiting the release of acetylcholine, a neurotransmitter. Since the approval of the product for strabismus and blepharospasm in US in 1989, the product is licensed for the treatment of various diseases, which respond to the muscle relaxant effects in more than 90 countries (as of Apr 2017).

In Japan, the product is licensed with 8 indications as an ethical drug so far: blepharospasm as first indication in Oct 1996, followed by “hemifacial spasm” in Jan 2000, “spasmodic torticollis” in Jun 2001, “talipes equinus associated with lower limb spasticity in paediatric patients two years of age and older with cerebral palsy” in Feb 2009, “upper limb spasticity” and “lower limb spasticity” in Oct 2010, “severe primary maschalephidrosis” in Nov 2012, and “strabismus” in Jun 2015. For “upper limb spasticity,” 240 units of the product is approved as a maximum dose per administration.

This study is a multicenter, double blind, placebo controlled phase III domestic study in patients with upper limb spasticity and aims to confirm the efficacy and safety of 240 units of the product for post-stroke upper limb spasticity. The information of 400 units of the product in the study is expected to provide beneficial information because the treatment with 240 units of the product with a maximum dose per administration is considered to be insufficient in some patients with post-stroke upper limb spasticity.

3.2. Background

Spasticity is a movement disorder that is characterized by increased myotatic reflex and is regarded as one of positive signs of the upper motor neuron signs (Kagamihara, 2012; Lance, 1980). Spasticity is caused by central nerve system injuries such as stroke, traumatic brain injury, or spinal cord injury and chronic neuropathies such as cerebral palsy or multiple sclerosis, etc. Abnormal postures of the upper limbs due to spasticity include thumb refraction, a clenched fist deformity, flexion of the wrist flexors, pronation of the forearms, flexion of the elbow flexors, and adduction/inner rotation of the shoulder flexors (Gracies, 2003; Kinoshita, 2015).

Spasticity hampers rehabilitation therapy. In addition, limitation of flexors range of motion and persistent pain hinder from caregiving and decrease activity in daily life (Grazko, 1995); therefore, many of patients with stroke require treatments to ameliorate their dysfunction.

For the treatments of spasticity, rehabilitation therapy, oral medications, phenol blocks, and baclofen injections were used until botulinum therapy has been approved as a national health insurance coverage. These treatments were commonly challenging because of lack of effects, difficult procedures, or invasive interventions. Subsequently, in Oct 2010, the product was approved as a botulinum treatment for upper and lower limb spasticity in Japan. Since then, botulinum toxin has been used for the treatment of spasticity (Ohsawa, 2013). According to the “Japanese Guidelines for the Management of Stroke” (initial version in 2009, revised in 2015) (Ogawa, 2015; Shinohara, 2009), which was issued by the Japan Stroke Society, botulinum therapy is recommended for the treatment of spasticity as Grade A, and is considered to be effective for relief of upper limb spasticity, increase of range of motions in flexors, and reduction of the amount of assistance on daily life.

In Japan, upper limb spasticity, a domestic phase II study involving the finger, wrist, and elbow flexors was performed from Dec 2001 through Mar 2003, and a domestic phase III study involving the finger and wrist flexors from May 2007 through Dec 2008. Consequently, the product was approved for the treatment of upper limb spasticity with a maximum dose of 240 units per administration in Oct 2010.

However, subsequently, the injections of the product at 240 units were found to be insufficient for the involving muscles because patients with extensive upper limb spasticity require dose adequate to inject into many of the involving muscles. Therefore, many medical institutions requested us to increase the maximum dose per administration of the product. Moreover, the specified drug-use survey from Jun 2011 through Apr 2014 identified that approximately 39% of the patients who use the product for upper limb spasticity were injected more than 240 units, a maximum dose per administration. The results suggest high patient needs for an increase of the maximum dose per administration of the product.

In US, as a maximum dose per administration, 400 units of injections of the product have been approved for the treatment of upper limb spasticity in adult patients in 2015; therefore, the authorized dose between US and Japan is different.

Based on these background, the study was planned to evaluate the efficacy and safety of 400 units of the product for upper limb spasticity in order to increase the maximum dose per administration to 400 units.

The study was planned based on the regulatory advice by the Pharmaceuticals and Medical Devices Agency (PMDA).

3.3. Benefit/Risk Assessment

For details of the known and anticipated benefit/risk and rationally expected adverse events are shown on the Investigator's Brochure (IB) and package insert.

3.3.1. Risk Assessment

| Important identified risks | Reports suggesting risks/ Outlines of rationale | Measures for risk minimization |
|--|--|--|
| Investigational product :GSK1358820 | | |
| Hypersensitivity | Serious and/or immediate hypersensitivity reactions (anaphylaxis, serum sickness, urticarial, soft tissue edema, or dyspnea, etc.) have been rarely reported. | Patients who previously experienced allergic reactions due to botulinum toxin type A, an additive agent of sodium chloride, or human serum albumin are excluded from enrolment. Upon written informed consent process, subjects will be explained that any urticarial, swelling face, throat swelling, wheezing, dizziness, or dyspnoea should contact their investigator. |
| Pre-existing neuromuscular disorder | Patients with neuromuscular junction diseases (myasthenia gravis, Lambert-Eaton myasthenic syndrome etc.) may increase the sensitivity to the product, resulting in excessive muscular weakness. | For patients with myasthenia gravis, Eaton-Lambert syndrome (ELS), amyotrophic lateral sclerosis, or a serious disease and who use a concomitant drug (s) which may inhibit neuromuscular function, exclusion criteria will be set, and those patients will be excluded from enrolment in the study (refer to 6.2.1). |
| distant spread of toxin | Adverse drug reactions in the remote muscles, except but the injected site, have been rarely reported. The adverse drug reactions include muscular weakness, constipation, dysuria, swallowing difficult, and non-accidental entering of food or fluid in the lungs not via the stomach, but the trachea (pneumonia may occur). The patients who received the product at a higher dose are considered likely to have increased risks for these adverse drug reactions. | In this study, a high dose of 400 units of the product will be injected. Therefore, the subjects will be followed up after 2, 4, 6, and 12 weeks of injection. The safety of the subjects will be observed carefully. Use of at least one of the following guide tools (electromyogram, electrical stimulator, or ultrasonography) will be essential in the blind phase to ensure identification of the exact site of injection. |

| Important identified risks | Reports suggesting risks/ Outlines of rationale | Measures for risk minimization |
|--|---|---|
| Immunogenicity, drug resistance, antibody production | The important cause of neutralizing antibody production has not been fully clarified. A few studies suggested that the injection of the product at short intervals or at a high dose may lead to increased rate of antibody production[Jankovic, 2006; Klein, 2002]. Neutralizing antibody production against botulinum toxin type A may lead to inactivation of the biological activity of the product, resulting in decreased therapeutic effects of the product. | In this study, patients who were considered likely to have neutralizing antibody production based on the previous treatment experience of botulinum toxin type A will be excluded from enrolment in the study (Exclusion Criteria 6.2.1). In addition, treatment schedule in the study was set to ensure at least a 12-week dosing interval. |
| Other (If applicable) | | |
| Medication error (preparation with lidocaine) | One fatal case due to anaphylaxis has been reported. In this case, the patient died after 100 units of an injection of the product that prepared inappropriately with 5 mL of 1% lidocaine. The causal relationship of death to the product and lidocaine, or both has been unknown. | In this study, the product will be prepared appropriately with 0.9% normal saline. The preparation method will be described on the study reference manual (SRM). |

3.3.2. Benefit Assessment

In patients with post-stroke upper limb spasticity, currently, the product is approved to inject up to 240 units per administration in Japan. However, in patients with extensive upper limb spasticity, the treatment effects of the product is presumed to lack because of the dose limitation.

In US, the efficacy and safety of the product up to 400 units per dose for patients with upper limb spasticity is confirmed, and the clinical use of the product has been approved. The injections of 400 units of the product in this study are expected to increase injectable sites and enhance the treatment effects in Japanese patients with upper limb spasticity, who did not have great benefits from 240 units of the product.

If a subject is assigned to the 240 units group in Part 1 and meets the eligibility criteria for injection in the open-label phase, 400 units of the product will be injected in and after Part 2. Therefore, all the subjects who participate in this study are given the opportunity to receive 400 units of the product (Refer to “[5. STUDY DESIGN](#)”).

3.3.3. Overall Benefit:Risk Conclusion

The known potential risks in the product is justified by the benefits which would provide for the patients with post-stroke upper limb spasticity, given the safety measures to minimize risks in subjects who enrol in the study.

4. OBJECTIVES AND ENDPOINTS

| Objectives | Endpoint(s) |
|--|--|
| Primary | |
| To evaluate the efficacy of injection of 400 units of the product at Week 6 (finger/ wrist flexors: 240 units, elbow flexors: 160 units), comparing to that of 240 units (finger/ wrist flexors: 240 units, elbow flexors: placebo). | The rate of the subjects that Modified Ashworth Scale (MAS) score was reduced at least 1 from baseline in the elbow flexors (the responder rate). |
| Secondary | |
| To evaluate the efficacy of 400 units of the product, comparing to 240 units of the product. | <ul style="list-style-type: none"> • The responder rate of MAS score from baseline in finger, thumb and wrist flexors • Changes in MAS score from baseline in finger, thumb, wrist, elbow, pronation of forearms and shoulder flexors • Changes in Disability Assessment Scale (DAS) from baseline |
| To evaluate the safety and tolerability of the product of 400 units, comparing to 240 units of the product/ To evaluate the safety and tolerability of 400 units of the product. | <ul style="list-style-type: none"> • Adverse events • Physical examinations • Clinical laboratory tests (haematology, blood biochemistry, urinalysis) • Vital signs (heart rate, blood pressure, body temperature) |
| Exploratory | |
| To evaluate the efficacy of 400 units of the product | <ul style="list-style-type: none"> • Changes in MAS score from baseline in finger, thumb, wrist, elbow, pronation of the forearm and shoulder flexors |
| To evaluate the other efficacy of the product of 400 units, comparing to 240 units of the product/ To evaluate the other efficacy of 400 units of the product | <ul style="list-style-type: none"> • Changes in Numeric Rating Scale (NRS) for pain from baseline • Changes in other items of DAS from baseline • Clinical Global Impression of Change (CGI) of functional disability by a investigator • CGI of functional disability by a patient • Time to patient-reported onset of spasticity symptom relief • Patient-reported benefit of injection • Time to qualification for retreatment |
| To evaluate neutralizing antibody production | <ul style="list-style-type: none"> • Testing for neutralizing antibody |

5. STUDY DESIGN

5.1. Overall Design

This study is a 48-week multicenter, phase III study (a placebo controlled, randomized, double-blind comparative study and an open-label, uncontrolled study) to evaluate the efficacy and safety of the product in patients with post-stroke upper limb spasticity. The study period is up to 52 weeks, consisting of a screening phase up to 4 weeks, minimum 12-week blind phase (Part 1), maximum 36-week open-label phase (12 weeks per cycle with maximum 3 treatment periods, Part 2, Part 3 and Part 4). (Figure 5).

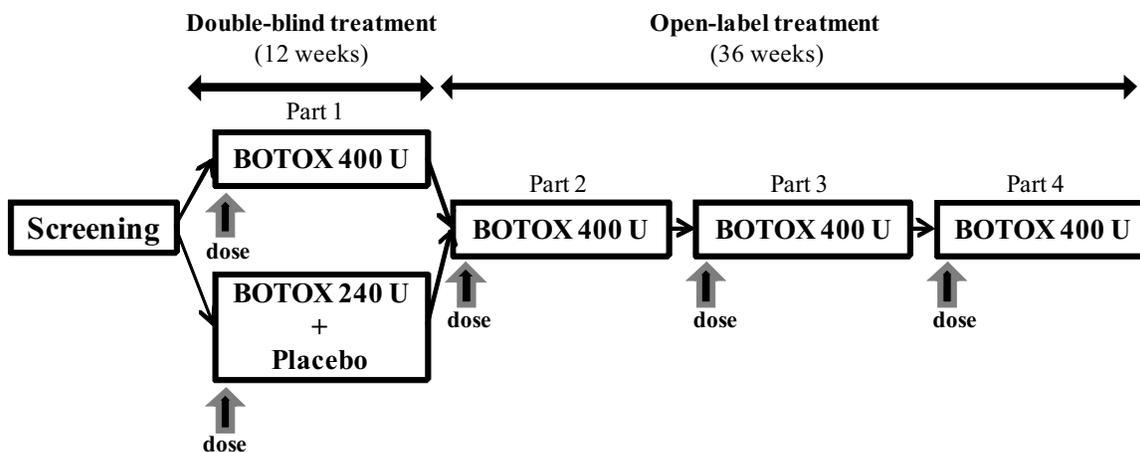


Figure 5 Study Design

In this study, the efficacy of 400 units of the product at Week 6 is evaluated, comparing to that of 240 units, and improvement tendencies are also evaluated in patients with post-stroke upper limb spasticity. The improvement will be defined as at least 1 reduction on the MAS score from baseline (a measurement value before injection of Day 1). The responder rate (the rate of the subjects that MAS score is reduced at least 1 from baseline) in the elbow flexors at Week 6 is set as an endpoint. As a point estimate, if the responder rate in the 400 units group outweighs that in the 240 units group, improvements tendencies will be considered to be positive.

For injection, use of the following any one of the tools: EMG, electrical stimulator, or ultrasonography, is recommended to ensure identification of the exact injection site. In the blind phase, use of at least one of the following tools: EMG, electrical stimulator, or ultrasonography, will be essential to ensure identification of the muscle to be injected correctly.

5.1.1. Screening Phase (up to 4 weeks)

Evaluation and screening tests will be performed 28 days to 7 days (+3 days) before initial injection (Day 1) as a starting point. The investigator will decide which arm to be injected during screening phase. Throughout the study period, the arm, which is decided to be injected at screening phase will be involved during the injections and evaluations, unless clearly specified otherwise by the sponsor.

5.1.2. **Blind Period (minimum 12 Weeks): Placebo Controlled, Randomized, Double Blind Design**

Subjects who meet the inclusion criteria will be randomized 1:1 to either the 400 units or the 240 units group.

- In the 400 units group, a total of 240 units of the product will be injected into the muscles that act on the finger (including thumb flexors) and wrist flexors, and a total of 160 units into the muscles that act on the elbow flexors; a total of 400 units of the product will be injected.
- In the 240 units group, a total of 240 units of the product will be injected into the muscles that act on the finger (including thumb flexors) and wrist flexors. Placebo will be injected into the muscles that act on the elbow flexors. A total of 240 units of the product will be injected.

If the total dose for the muscles that act on the finger and wrists flexors is ensured by 240 units, and 160 units for the muscles that act on the elbow flexors, the dose can be adjusted at an investigator's discretion based on the subject's symptoms. (Refer to "7.1. Treatments Administered" Table 2).

5.1.3. **Open-Label Phase (maximum 36 weeks): Uncontrolled, Open-Label Design**

The product of 400 units will be injected in both groups. The product can be injected up to 3 times after completion of Part 1 in the blind phase. In the open-label phase, subjects whom the investigator considers eligible for the injection will be treated (Refer to 5.1.3.1. Eligibility Criteria for Injection in and after Part 2). The next injection cannot be performed until the eligibility of the subject has been confirmed by the investigator (Refer to 5.1.3.1. Eligibility Criteria for Injection in and after Part 2).

In the open-label phase, the muscle to be injected and the dose will be decided by the investigator based on the patient's symptoms, and a total dose of 400 units of the product will be injected in a divided dose (Refer to "7.1. Treatments Administered" on Table 3). For the muscles that the investigator considers unnecessary to be treated, an injection may be skipped. The involving muscle and the dose do not have to be the same each time always.

5.1.3.1. **Eligibility Criteria for Injection in and after Part 2**

In the open-label phase (Part 2, Part 3, and Part 4), the subjects whom the investigator considers eligible for the injections in the open-label phase only will be treated. The eligibility is evaluated at a study visit after Week 12 (V5, if a subject does not meet the eligibility criteria, the evaluation will be performed at QRV (Qualification for Retreatment Visit). A subject will be considered as eligible when he or she meets all the criteria. The eligibility evaluation will be performed after completion of Part 1 in the blind phase, between Week 12 to Week 36. If a subject does not meet the eligibility at Week 36, subsequent evaluation will not be performed, and the product cannot be given (refer to Figure 1, Figure 2, Figure 3, and Figure 4).

- 1) At least 12 weeks (84 days) have passed since the preceding dose
- 2) Among the finger, wrist or elbow flexors, 2 flexors have at least 2 on the MAS (except only the finger and wrist flexors of 2 on the MAS)
- 3) Subject who request the injection

- 4) Subjects whom a investigator considers an injection of 400 units of the product is appropriate
- 5) Subjects who have not experienced serious adverse events (SAE) associated with the injection of the product

If subjects meet the criteria of the above 1) to 5) at V5 or QRV, body weight measurement, ECG, pulmonary function test, and pregnancy test will be performed to evaluate the following items. If subjects meet the following 6) to 8), the subjects will move forward to V1.

Pulmonary function test must be performed at V5 even if subjects do not meet the above 1) to 5) in accordance with the study operation schedule (SoA).

- 1) Body weight ≥ 40 kg
- 2) Subjects who the investigator considers there are no unacceptable safety concerns [potential for serious adverse events, laboratory data (V5), electrocardiogram (ECG) or pulmonary function value] due to 400 U of BOTOX
- 3) Woman of childbearing potential who have negative pregnancy test result in urine

5.2. Number of Participants

Approximately 120 subjects (approximately 60 in each group) will be randomized to obtain an evaluable subject sample of approximately 100 at Week 48 as subjects who complete the study

5.3. Participant and Study Completion

Subjects who completed all the study procedures, including a completion visit will be regarded as study completion. The completion date in this study will be defined as the last day performing the study procedure of last subject.

5.4. Scientific Rationale for Study

The study design was set to evaluate the efficacy and safety of 400 units of the product in patients with post-stroke upper limb spasticity. The primary endpoints employed the responder rate of the MAS score in the elbow flexors. The reasons for employing MAS score as an indicator include that MAS is highly reliable for evaluation of upper limb spasticity ([Bohannon, 1987](#); [Mutlu, 2008](#)); especially, for evaluation of spasticity in the elbow flexors in the upper limbs ([Gregson, 2000](#); [Sloan, 1992](#)).

Screening Phase

The screening phase up to 28 days before initial injection was set in order to confirm subjects meet the inclusion criteria and none of the exclusion criteria, and assess the condition of subjects at baseline. However, measurements of laboratory parameters at screening phase should be completed by 4 days before Day 1 (Day -28 to -4).

Treatment Phase

In Part 1, a double blind comparative study was set to compare the efficacy of the product of 400 units to 240 units, the currently approved dose for upper limb spasticity. In the blind phase, 240 units

of the product will be injected into the muscles that act on the finger (including the thumb)/wrist flexors, and 160 units (the 400 units group) or placebo (the 240 units group) for the muscles that act on the elbow flexors. The improvement tendencies in the efficacy between the 240 units group, the total dose, and the 400 units groups will be compared by evaluating the responder rate tendencies on the MAS score in the elbow flexors in a blinded manner. In the previous confirmatory study (108509 study) for approval of the product for upper limb spasticity, the elbow flexors were not involved. Therefore, in this study, the responder rate on the MAS score in the elbow flexors was decided to compare as the placebo group.

Actually, in medical institutions, the product is injected into the whole upper limb, including the shoulder flexors. In addition, the dose for each muscle is decided at a investigator's discretion. Previous studies reported that botulinum injections into the pectoralis major and teres major muscle relieved pain in patients with hemiplegia (Marciniak, 2012) and injections into the sub-scapula improved passive range of motion (Yelnik, 2007). Therefore, in and after Part 2 in the open-label phase, the product will be allowed to be injected not only into the muscles that acts to the finger (including the thumb), wrist, and elbow flexors, but also the muscles that act on the shoulder flexors, where applicable, enabling a investigator to decide the dose for each muscle. In addition, the study design included safety evaluation of the product at Week 48 after initial injection in all subjects as far as possible for safety evaluation purposes of 400 units.

5.5. Dose Justification

The product of 400 units is a maximum dose for upper limb spasticity, which was approved by the U.S. Food and Drug Administration (FDA), and this suggests that the efficacy and safety profiles are favourable. Evaluation of the efficacy and safety of 400 units of the product provides beneficial information in Japanese patients with severe post-stroke upper limb spasticity, who are considered injections of 400 units of the product are necessary.

The dose of 240 units of the product, the controlled group, in the blind phase (Part 1) is the current authorized dose (a maximum dose per administration) for upper limb spasticity in Japan. In this study, the 240 units group was set as the control group in order to evaluate improvement tendencies, comparing the efficacy of 240 units of the product, the current approved dose, to that of 400 units of the product.

6. STUDY POPULATION

Inclusion of subjects despite expectation of deviation from the protocol, namely, exemption or discharge from the protocol, cannot be allowed.

6.1. Inclusion Criteria

6.1.1. Screening Phase (Day -28 to Day -1)

In the screening phase, subjects eligible for enrolment in the study must meet all of the following criteria. Laboratory parameters should be measured by 7 days (± 3 days) before initial injection (Day 1).

Age

1. Between 20 and 80 years of age at the time of informed consent (ICF).

Subjects and Characteristics of the Disease

2. Patients with at least a 3-month history of upper limb spasticity after the most recent stroke
3. Patients who have spastic symptoms in the finger (including the thumb), wrist, and elbow flexors whom the investigator considers the injections of 400 units of the product is necessary for the upper limb based on the muscle spasms and the symptoms of the patient
4. Patients who have a previous treatment history of 240 units of the product for the upper limb at least 16 weeks before screening (refer to [Table 3](#) for muscles in the upper limbs)
5. Patients who meet following criteria on MAS at screening (Test position : sitting)
 - At least 3 in for the elbow flexors
And
 - At least 2 in the finger or wrist flexors
6. Patients who have severe upper limb spasticity, which deserves to be treated with 400 units of the product in the divided dose and was previously injected 240 units of the product
7. Patients whom the investigator considers that enrolment in the study poses no problems based on the laboratory data results at screening
8. Patients who are free from a history of acute decreased lung function (hospitalization with aggravated asthma/COPD, pneumonia, or signs of pneumonia, or abnormal reactive airway diseases suggested on X-rays) within the last 3 months at screening and have stable pulmonary function (SpO₂ [oxygen saturation] value is $\geq 95\%$)

Body Weight

9. Body weight ≥ 40 kg at screening

Sex

10. Male or female

a. Male Subjects

Male subjects must content to use highly effective contraceptive methods, which are shown on attachment 5 of the protocol in detail during the study period, and sperm donation must be avoided.

b. Female Subjects

Female subjects who are not pregnant or lactating are considered eligible (refer to attachment 5) if at least one of the following criteria is met:

- i) Non-childbearing potential based on the definition on attachment 5
- ii) Women of childbearing potential who content to follow the guidance about contraception on attachment 5 during the study period and at least for 3 months after the last dose of the product.
- iii) No plan of pregnancy during the study period

Informed Consent

11. Patients who have ability to sign their name on the ICF, following the description on attachment 3, adhering to the requirements and limitations described on the ICF and the protocol.

6.1.2. Day 1 (prior to injection)

Subjects eligible for enrolment in the study must meet all of the following criteria on Day 1 (prior to injection):

Subjects and Characteristics of the Disease

31. Patients who meet the following criteria on MAS score: (Test position : sitting)
- At least 3 in the elbow flexors
- And
- At least 2 in the finger or wrist flexors

Preceding Treatments and Concomitant Medications/Therapies

32. If centrally acting muscle relaxants, tetracycline antibiotics, anticholinergics, benzodiazepines, or benzamides are given, the dose and regimen must be stable at least for the last 2 months before Day 1; Patients who can maintain the same dosage and regimens at least in the blind phase after initial injection (dose reductions and discontinuation of the drugs are acceptable in the open-label phase. However, second dose increase, resumption, and or new treatment will not be performed).
33. If intrathecal baclofen is given, the dose and regimen must be stable at least for the last 1 month before Day 1; Patients who can maintain the same dosage and regimens at least in the blind phase after initial injection (intravenous bolus is not acceptable, dose reductions and discontinuation of the drugs are acceptable. However, second dose increase, resumption, and or new treatment will not be performed).
34. If antiepileptic agents are given, the dose and regimen must be stable at least for the 1 month before Day 1; Patients who can maintain the same dose and regimens at least in the blind phase after initial injection (dose reductions and discontinuation of the drugs are acceptable in the open-label phase. However, second dose increase, resumption, and new treatment will not be performed).
35. If a physical therapy, occupational therapy, or a static splint on the study involvement upper limbs is given, the frequency and treatment regimen must be stable at least for the last 3 weeks before Day 1; Patients who can maintain the same dose and regimens at least in blind phase (In the open-label phase, the frequency and treatment regimen can be changed depending on the condition of spasticity).

6.2. Exclusion Criteria

6.2.1. Screening Phase (Day -28 to Day -1)

A subject will be excluded from enrolment in this study if any of the following criteria apply in the screening phase. Measurements of laboratory parameters at screening must be completed 7 days (± 3 days) before initial injection (Day 1).

Medical Condition

1. Patients present with spasticity requiring treatment in the non-paralytic side of the upper limb
2. Patients who have fixed contracture* in the finger (upper limb), wrist, elbow or shoulder muscle, which will be involved in the study

(*Positive effects were not confirmed in the previous treatment with GSK1358820, and contracture is considered to be the main cause of limited range of motion in the joint.)

3. Patients who have medically significant capsulitis or subluxation in any one of the fingers (upper limb), wrist, elbow and shoulder, which will be involved in the study, or whom a investigator considers the complicated local signs of pain may affect the efficacy evaluation
4. Patient's upper limb spasticity is attributed to other than stroke (traumatic brain injury, spinal cord injury, multiple sclerosis, or cerebral palsy)
5. Patients who have a 2-fold higher alanine aminotransferase (ALT) level than the upper limit of normal (ULN)
6. Patients who have a 1.5-fold higher bilirubin than the ULN (If a bilirubin fractionation shows direct bilirubin < 35%, a 1.5-fold higher free bilirubin than the ULN is acceptable).
7. Patients whom the investigator considers presence of a current medical history of unstable liver diseases or biliary tract diseases (the condition will be defined by development of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice or hepatic cirrhosis)

Note:

- If a patient with stable chronic liver diseases (Gilbert's syndrome, silent gallstone, and stable chronic hepatitis B or hepatitis C [Namely, hepatitis B surface antigen: HBsAg or hepatitis C virus: HCV antibody shows positive at screening or within 3 months before initiation of the study treatment] are included) meets other inclusion criteria, the patient can be enrolled in the study.

8. Patients with QTc > 450 msec or QTc > 480 msec in patients with bundle branch block

Note:

- QT intervals corrected by the Bazett method (QTcB); QT intervals corrected by the Fridericia method (QTcF) and/or QT intervals corrected by other methods; interpretation by a machine or manual re-interpretation will be used.
- Prior to study initiation, the correction formula which is used for the subject's inclusion/exclusion/discontinuation criteria will be determined. Namely, several different correction formula cannot be used for calculation of QTc in each subject. In addition, the lowest QTc level cannot be used for enrolment or discontinuation of subjects of the study.

Preceding Treatments and Concomitant Medications/Therapies

9. Patients who use peripherally acting muscle relaxants (dantrolene sodium, suxamethonium chloride, pancuronium bromide, vecuronium bromide, rocuronium bromide, etc.) within 1 week of screening.
10. Patients who use antibiotic agents with neuromuscular junction inhibitory effects: Aminoglycoside antibiotic agents (streptomycin sulfate, kanamycin sulfate, gentamicin sulfate, neomycin sulfate, spectinomycin hydrochloride, etc.), polypeptides (polymyxin B sulfate), lincomycins (lincomycin hydrochloride, clindamycin), and enviomycin sulfate within 1 week of screening.
11. Patients who was diagnosed as having a malignant tumor, or have a history of a malignant tumor within the last 5 years (except completely resected basal cell carcinoma or planocellular carcinoma at least 12 weeks before screening)

Previous Experience of Participation in a Clinical Studies/Current Participation in another Ongoing Study

12. Patients who have participated in another study of an investigational product or other medical research (a clinical study of pharmacotherapy, non-pharmacotherapy, or interventional device) within 30 days before screening, or are currently participating in a study

Evaluation by Diagnosis

13. Patients who are concerned likely to have an increased risk for an underlying medical condition/neurological disease due to exposure of the product; patients who have myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or a serious disease and use of a concomitant drug which may inhibit neuromuscular function
14. Patients with antihuman immunodeficiency virus (HIV) antibody positive
15. Patients who previously experienced allergic reactions or hypersensitivity due to botulinum toxin type A, an additive agent of sodium chloride, or human serum albumin
16. Patients who were previously suspected to have neutralizing antibody production by an investigator during an injection of botulinum toxin type A
17. Patients who have a skin disease such as infection at the site to be injected
18. Patients who suffer from serious and unstable disease, which could pose problems for the safety of subjects and study procedure compliance

6.2.2. Day 1 (Prior to injection)

A subject will be excluded from enrolment in this study if any of the following criteria apply on Day 1 (prior to injection):

Medical condition

31. Patients who have aspiration pneumonia, relapse of lower respiratory tract infection, uncontrollable asthma, uncontrollable COPD, and/or underlying or a history of serious respiratory dysfunction, which were clinically considered to be respiratory function impairment by an investigator within 12 months before Day 1 visit
32. Patients who have a history of aspiration, or an underlying and/or a history of the symptoms that suggests high risks for aspiration by an investigator within 12 months before Day 1 (serious salivation requiring changing in a type of diet, chronic dysphagia that is difficult to swallow)

Preceding Treatments and Concomitant Medications/Therapies

33. Patients who were treated with botulinum toxin for spasticity of upper limb less than 16 weeks before Day 1 visit
34. Patients who underwent surgical interventions, phenol block, ethanol block or Muscle Afferent Block (MAB) within 12 months before Day 1 visit, or these interventions are planned during the study period in any one of the finger (upper limb), wrist, elbow or shoulder muscles, which will be involved in the study
35. Patients who placed a surgical cast or a dynamic splint within 3 months before Day 1 study visit, and/or these interventions are planned to be placed on the upper limb to be involved in the study

36. Patients who were injected corticosteroid or an anesthetic agent into the finger (upper limb), wrist, or shoulder flexors, which will be involved in the study within 3 months before Day 1 visit, or these injections are planned during the study
37. Patients who received CIMT (constraint-induced movement therapy) within 3 months before Day 1 visit or CIMT is planned during the blind phase
38. Patients who underwent ultrasound therapy, TENS (transcutaneous electrical nerve stimulation), electrical stimulation therapy, or acupuncture therapy in the upper arm, which will be involved in the study within 1 month before Day 1 visit, or these therapies are planned during the study

6.3. Lifestyle Restrictions

No limitations are required.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently [randomized/entered in the study]. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Rescreening

If a patient does not meet the participation criteria in the study (dropout during screening), the patient may undergo second screening only 1 time. If a patient does not meet following items, contact the medical monitor of the sponsor and gain his/her consent because validity of rescreening in subjects who dropped out needs to be judged carefully in the light of medical aspects.

- Subjects who did not meet the inclusion criteria for MAS (Inclusion criteria 5 at screening) and dropped out (However, the dropout period will be for within only 1 month from the dropout).
- For some reasons, a subject cannot make a study visit or undergo examination
- Sample collection or examination cannot be performed because of procedural or technical problems

The investigator must carefully consider the ethical aspects of subjects, and if other treatments are considered to give more treatment benefits for a subject, rescreening must not be conducted.

The rescreened subjects will be allocated a different subject identification number as upon initial screening.

7. TREATMENTS

Study treatment product is defined as any investigational treatment(s), and placebo to administer to a study participant according to the protocol.

7.1. Treatments Administered

| | | | |
|---|--|-----------|---|
| Study Treatment Name: | GSK1358820 (Nonproprietary name: Botulinum toxin type A) | | Placebo |
| Dosage formulation: | Injection | | Injection |
| Ingredient and quantity (Per vial) | Botulinum toxin A 100 units Sodium chloride 0.9 mg Human serum albumin 0.5 mg | | Sodium chloride 0.9 mg |
| Packaging and Labeling | It will be listed on the labelling in accordance with the regulatory requirements in Japan. | | It will be listed on the labelling in accordance with the regulatory requirements in Japan. |
| Manufacturer | Allergan (Ireland) | | Allergan (Ireland) |
| Dose | 400 units | 240 units | Dose |
| Dosing instructions | <p>Part 1: 240 or 400 units of the product will be injected into the muscles that act on the finger (including thumb flexors), wrist and elbow flexors, in accordance with Table 2. In and after Part 2: 400 units of the product will be injected into the muscles that act on the finger (including thumb flexors), wrist, elbow and shoulder flexors in accordance with Table 3. For the muscles that the investigator considers unnecessary to be treated, an injection may be skipped. Dose intervals should be at least 12 weeks.</p> <p>For adjustment of the product, the product will be dissolved with 2 ml of normal saline per 1 vial (100 units). The details will be described on Table 4.</p> | | |

In the blind phase

- A total of 240 units of product will be injected into the muscles that act on finger (including thumb flexors) and wrist flexors, and a total of 160 units of the product or placebo for the muscles that act on the elbow flexors in divided doses in accordance with [Table 2](#).
- The muscles which are not listed on [Table 2](#) must not be used.
- All of the muscles described on [Table 2](#) must be used. If the subject with no symptoms with thumb, the investigator does not have to inject to thumb.
- If the total dose for the muscles that act on the finger and wrists flexors is ensured by 240 units, and 160 units for the muscles that act on the elbow flexors, the dose can be adjusted at an investigator's discretion based on the symptoms of a subject.

In the open-label phase

- The investigator will decide the dose and the muscle to be injected based on the symptoms of patients, and a total of 400 units will be injected in divided doses. For the muscles that the investigator considers unnecessary to be treated, an injection may be skipped.
- The muscles to be injected must be chosen from [Table 3](#), and the muscles which are not listed on [Table 3](#) must not be used. For dose and number of injection site (sites/muscles), refer to [Table 3](#) and will be decided by investigator.

Table 2 Muscle Involvement and Dose in the Blind Phase

| Number | Muscles | The 400 units group Dose (units) | The 240 units group Dose (units) | Number of injection site (site and muscles) ³ | Joint |
|--------|--------------------------------|----------------------------------|----------------------------------|--|----------|
| A1 | Biceps brachii | 70 ¹ | Placebo | 2 | A.Elbow |
| A2 | Brachialis | 45 ¹ | | 1 | |
| A3 | Brachioradialis | 45 ¹ | | 1 | |
| B1 | Flexor carpi radialis | 50 ² | 50 ² | 1 | B.Wrist |
| B2 | Flexor carpi ulnaris | 50 ² | 50 ² | 1 | |
| C1 | Flexor digitorum profundus | 50 ² | 50 ² | 1 | C.Finger |
| C2 | Flexor digitorum superficialis | 50 ² | 50 ² | 1 | |
| D1 | Flexor pollicis longus | 20 ² | 20 ² | 1 | D.Thumb |
| D2 | Adductor pollicis | 20 ² | 20 ² | 1 | |
| | Total | 400 ² | 240 ² | 1 | - |

1: Within the limits of the total of 160 units (the elbow flexors), the dose will be decided by a investigator depending on the patient's symptoms.

2: Within the limits of the total of 240 units (the finger and wrist flexors), the dose will be decided by a investigator depending on the patient's symptoms.

3: When the dose exceeds 50 U per muscle, take into account the divided-injection.

Table 3 Muscle Involvement and Reference Dose in the Open-Label Phase
(Modified partially of "Dosing, Administration, and a Treatment Algorithm for Use of Botulinum Toxin A for Adult-Onset Spasticity.[Brin, 1997]")

| Number | Muscles ¹ | Dose (units) ² | Number of injection site (Sites/muscles) ² | Joint |
|--------|--------------------------------|---------------------------|---|------------|
| A1 | Biceps brachii | 50-200 | 4 | A.Elbow |
| A2 | Brachialis | 25-75 | 2 | |
| A3 | Brachioradialis | 25-75 | 2 | |
| B1 | Flexor carpi radialis | 25-100 | 2 | B.Wrist |
| B2 | Flexor carpi ulnaris | 10-50 | 2 | |
| C1 | Flexor digitorum profundus | 25-100 | 2 | C.Finger |
| C2 | Flexor digitorum superficialis | 25-75 | 4 | |
| C3 | Lumbricales interossei | 10-50/hand | 3 | |
| D1 | Flexor pollicis longus | 5-25 | 1 | D.Thumb |
| D2 | Adductor pollicis | 5-25 | 1 | |
| D3 | Opponens | 5-25 | 1 | |
| E1 | Pronator teres | 25-75 | 1 | E.Forearms |
| E2 | Pronator quadratus | 10-50 | 1 | |
| F1 | Teres major | 25-75 | 1 | F.Shoulder |
| F2 | Latissimus dorsi | 50-150 | 4 | |
| F3 | Pectoralis major | 75-150 | 4 | |
| F4 | Subscapularis | 25-75 | 1 | |

(Brin MF and the Spasticity Study Group, 1997)

1: The muscles which are not listed on Table 3 must not be used

2: For dose and number of injection site (sites/muscles), refer to Table 3 and will be decided by investigator.

Table 4 Muscle Involvement and Reference Dose in the Open-Label Phase

| Dose (units) | Injection Volume (ml) |
|--------------|-----------------------|
| 100 | 2.0 |
| 95 | 1.9 |
| 90 | 1.8 |
| 85 | 1.7 |
| 80 | 1.6 |
| 75 | 1.5 |
| 70 | 1.4 |
| 65 | 1.3 |
| 60 | 1.2 |
| 55 | 1.1 |
| 50 | 1.0 |
| 45 | 0.9 |
| 40 | 0.8 |
| 35 | 0.7 |
| 30 | 0.6 |
| 25 | 0.5 |
| 20 | 0.4 |
| 15 | 0.3 |
| 10 | 0.2 |
| 5 | 0.1 |

7.2. Dose Modification

Not applicable

7.3. Method of Treatment Assignment

After completion of all evaluations at screening phase/initiation of the blind phase, the subjects who met the inclusion criteria and none of the exclusion criteria will be given their randomization number at a case registry center and randomized to either the 240 or 400 units group. The assigned randomization number cannot be re-used. The table of the allocation will be prepared via a computer in GSK, using the RandAll systems.

Based on the MAS score (3 or 4) in the elbow flexors, subjects will be stratified at the time of randomization.

The subjects who meet the eligibility for the injections in the open-label phase can move forward to the open-label phase and be injected (Refer to section 5.1.3). In the open-label phase, 400 units of the product will be given to all subjects. Other detailed information will be described on SRM.

7.4. Blinding

This study consists of the blind phase (Part 1), followed by the open-label phase (Part 2 and subsequent Parts), and in the blind phase, following processes are applied.

A Role of the Person Responsible for Investigational Product Assignment

The person who is responsible for investigational product assignment will prepare an operating procedure for the assignment. The operation will be conducted in accordance with the operating procedure. The person who is responsible for the investigational product assignment will display the drug number on a container of the investigational product (investigational product and control drug)

after checking of the investigational product (investigational product and control drug) and the indistinguishability of packaging appearance. The confirmation of the investigational product (investigational product and control drug) and the indistinguishability of packaging appearance will be also performed after completion of the study. In addition, an operating procedure for occasion where the emergency treatment disclosure is required will be prepared. In response to the request of disclosure, unblinding procedures are performed for the requested drug only.

The unblinded subjects by the investigator will discontinue participation in the study. In addition, the major reasons for discontinuation (the event(s) or condition led to unblinding) will be described on case report form (CRF).

The Global Clinical Safety and Pharmacovigilance (GCSP) of the sponsor may disclose the assigned treatment in the subject, who experienced serious adverse events. For serious adverse events requiring emergency report to the regulatory authority, a copy of an emergency report on the assigned treatment of the subject may be sent to the study involving investigator in accordance with the regulations, policy of the sponsor, or both.

7.5. Preparation/Handling/Storage/Control

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual

7.6. Treatment Compliance

Subjects will be intramuscularly injected the product at a medical institution. The injection will be recorded in the source documents, and described in the case report form.

7.7. Concomitant Therapies

The medications that are used by subjects at the time of enrolment in the study or all medications and vaccines to be used during the study (over the counter drugs or prescribed drugs, vitamins, and/or herbal supplements) must be recoded with the following items:

- Reasons for use
- Initial date of administration and administration dates, including completion day
- Regarding the dose, including dosage and number of administration

Contact the medical monitor if there are any questions about concomitant therapies or preceding drugs.

7.7.1. Permitted Concomitant Drugs/Therapies

Following drugs and therapies are permissible only if a subject is already using them before initiation of the study. However, the dosage and administration will not be changed from the screening through completion of the blind phase. In and after open-label phase, dose reduction and discontinuation of the drugs will be allowed. However, once dose is decreased, re-increase will not be performed. If the drug(s) is/are discontinued, the drugs cannot be resumed. No new treatment will not be started after screening phase.

Rehabilitation therapies such as physical therapy, occupational therapy, and static splint are permissible. However, in the blind phase, the frequency and regimens (description of the therapy and intensiveness) for the upper limb, which involves in the study will not be changed. In addition, in the open-label phase, changing rehabilitation therapy to another one that seems to be the most appropriate for a subject is permissible based on the degree of improvements in spasticity. In such cases, the information will be described on CRF. Rehabilitation therapy will not be given on the day of investigational product injection.

- Central muscle relaxants
(baclofen, tizanidine hydrochloride, tolperisone hydrochloride, eperisone hydrochloride, chlorphenesin carbamate, afloqualone, etc.)
- Tetracycline antibiotics
(tetracycline hydrochloride, doxycycline hydrochloride, minocycline hydrochloride, etc.)
- Anticholinergics
(butylscopolammonium bromide, trihexyphenidyl hydrochloride, etc.)
- Benzodiazepines
(diazepam, etizolam, etc.)
- Benzamides
(tiapride hydrochloride, sulpiride, etc.)
- Antiepileptic drugs
(phenytoin, etc.)
- Intrathecal baclofen therapy

7.7.2. Contraindicated Medications/Therapies

Following drugs and therapies will be prohibited to use from screening phase through completion of the study:

- Botulinum toxin preparations
- Peripherally acting muscle relaxants
(dantrolene sodium, suxamethonium chloride, pancuronium bromide, vecuronium bromide, rocuronium bromide)
- Antibiotic agents with neuromuscular junction blocking effects
 - Aminoglycosides
(streptomycin sulfate, kanamycin sulfate, gentamicin sulfate, neomycin sulfate, spectinomycin hydrochloride, etc.)

- Polypeptides
(polymyxin B sulfate)
- Lincomycins
(lincomycin hydrochloride, clindamycin)
- Enviomycin sulfate
- Nerve blocks such as phenol block, ethanol block and MAB for the upper limb
- Surgical cast or a dynamic splint
- A surgery for the upper limb
- A surgical cast or a dynamic splint for the upper limb
- Corticosteroid injection or an anesthetic agent for the upper limb
- Ultrasound therapy, TENS (transcutaneous electrical nerve stimulation), electrical stimulation therapy, or acupuncture therapy for the upper limb

Following drugs and therapies will be prohibited to use from screening phase through completion of the blinded-phase:

- CIMT (constraint-induced movement therapy)

7.8. Treatments after Completion of the Study

The investigator will take responsibility for subject's medical care after completion of the study, whether the sponsor provides a certain treatment or not.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

The efficacy of the investigational product used in this study sustains for about 3 to 4 months following a single dose, and thus daily dosage is not required; accordingly, treatment discontinuation shall not be defined in this study, and will be considered to be identical to subject withdrawal from this study.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- A subject discontinuing this study must visit the study site for study termination assessment promptly upon decision to discontinue the study.
- Refer to the schedule of assessment (SoA), completion visit (FV), for the details of data to be collected at the study discontinuation, and additional assessment that must be completed.

8.2.1. Liver Chemistry Stopping Criteria

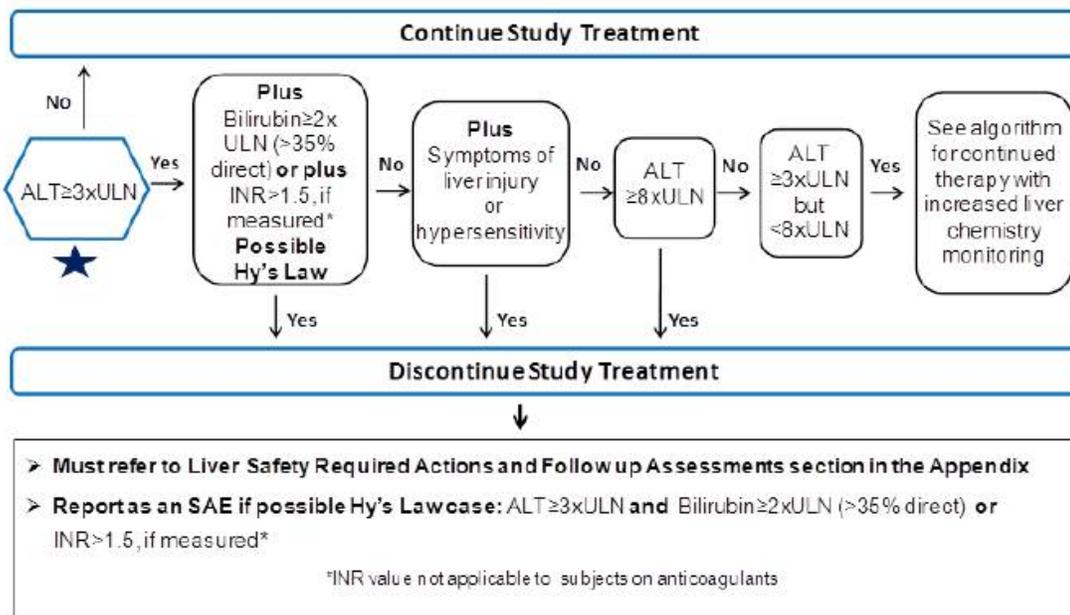
A set of criteria for **study discontinuation and follow-up investigation based on hepatic function test** (in reference to FDA premarketing clinical liver safety guidance) is specified herein to ensure the safety of subjects and to evaluate the causes of hepatic events. The guidelines related to this protocol are based on the FDA premarketing clinical liver safety guidance:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>.

The investigator should consider discontinuing the study treatment upon discovery of liver function test abnormal, and if the subject is applicable to any of the symptoms presented in the algorithm, or such discontinuation is determined to be the best choice for the subject as judged by the investigator.

Algorithm A: Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm

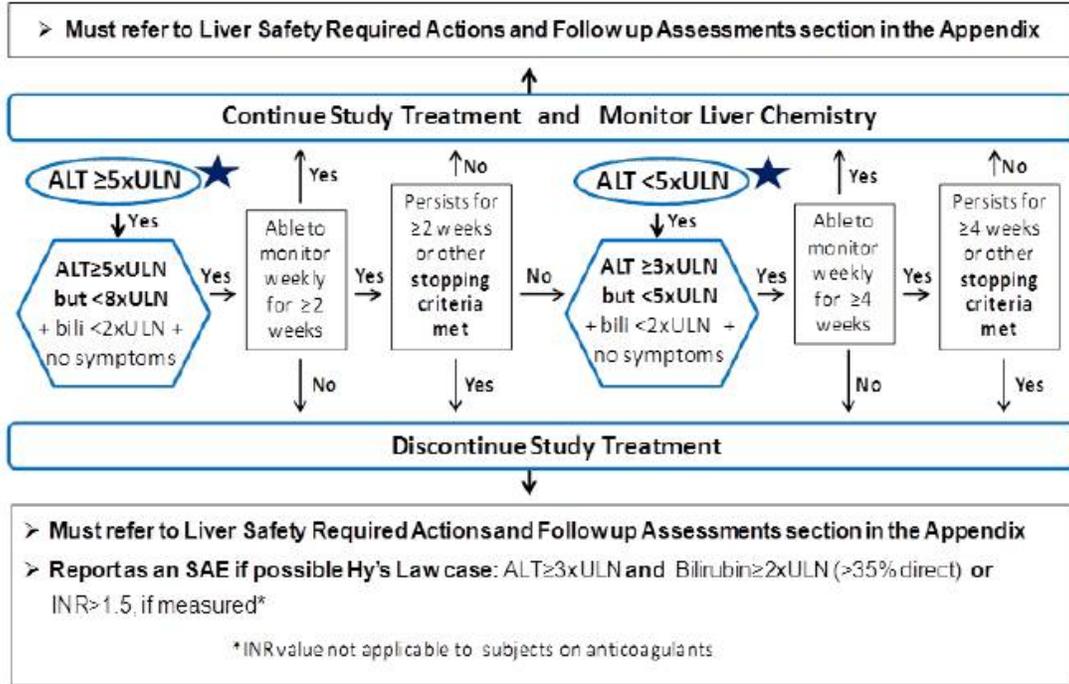
Algorithm A: Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

Algorithm B: Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT $\geq 3xULN$ but $< 8xULN$

Algorithm B: Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT $\geq 3xULN$ but $< 8xULN$



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

8.2.2. QTc Stopping Criteria

- For a decision on a subject's eligibility or study discontinuation, the same method for correction of QT interval must be used in the subject throughout the study, and must not be changed once the subject is enrolled.
 - For instance, if a subject is enrolled based on QTcB, decisions on the subject's withdrawal must be made based on QTcB.
 - The method used for correction of QT interval pertinent to the enrollment of a subject must be used for all QTc data to be collected throughout the study for the data analysis on the subject; provided that such rule is not applicable to ECG intended to ensure safety and also ECG not defined in the protocol.
- QTc should be determined based on a single measurement of ECG or the mean of ECG measured at 3 timepoints in a short period of time (e.g., 5 to 10 minutes). If abnormality is detected in a single measurement, ECG should be measured again, this time, at 3 timepoints.
- The lowest value of QTc cannot be used for a decision to withdraw a subject.

Refer to the schedule of assessment (SoA), completion visit (FV), for the details of data to be collected at the discontinuation of study treatment. Discontinue this study if the mean ECG is applicable to any of the following conditions:

- QTc >500 msec or uncorrected QT >600 msec
- Change in QTc from baseline >60 msec

The following withdrawal criteria should be applied for subjects with bundle branch block:

| Baseline for subjects with bundle branch block | Withdrawal criteria for subjects with bundle branch block |
|--|---|
| <450 msec | >500 msec |
| 450 to 480msec | IJYO530 msec |

8.2.3. Treatment discontinuation due to treatment-related SAE

A subject should be withdrawn from this study if treatment-related serious adverse event has occurred.

8.2.4. Treatment discontinuation due to pregnancy

A female subject who become pregnant during this study must be withdrawn from the study.

8.2.5. Withdrawal of subjects who start receiving prohibited medications or therapies

If a prohibited medication or therapy (See section 7.7.2.) needs to be started during the study, the subject must be withdrawn from this study; in which case, the subject must make the study completion visit (FV) before starting the prohibited medication or therapy.

8.2.6. Prohibition of treatment resumption

Study treatment must not be resumed in subjects who are once withdrawn from this study for a reason associated with hepatic function test, QTc, treatment-related serious adverse event, pregnancy, or commencement of a prohibited medication or therapy.

8.3. Lost to follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.

9.1. Efficacy assessments

9.1.1. Evaluation methods

9.1.1.1. Modified Ashworth Scale (MAS)

According to "2. SCHEDULE OF ACTIVITIES (SoA)" the investigator will use MAS (Table 5) to evaluate the level of spasticity. MAS should be measured and evaluated by the investigator, physiotherapist, or occupational therapist who has been given the training as an assessor.

The test should be performed on sitting position throughout the study. The affected parts should be extended as fast as possible to grade the flexor muscle tones. The final assessment will be made by the investigator in consideration of the information from physiotherapist or occupational therapist. The assessor should in principle remain unchanged throughout the study period.

Table 5 Modified Ashworth Scale (MAS)

| | |
|----|---|
| 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 ROM (range of movement) |
| 2 | More marked increase in muscle tone through most of the ROM, 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 measurement as inclusion criteria (Screening and Day 1)

The subject's wrist or fingers and elbow should all be evaluated as inclusion criteria. Subjects meeting the eligibility and randomized should be evaluated for MAS at Visit 1 of Treatment Period 1 on the same day; provided that measurement may be performed only once if the affected part to be evaluated is the same. The detail of inclusion criteria are shown in 6.1.

- MAS measurement during the blinded period

The subject's wrist, fingers and thumb should all be evaluated during the blinded period. Likewise, the subject's wrist, fingers and thumb should all be evaluated for MAS at Visit 5 and QRV of the blinded period. Subjects meeting the eligibility and transferred to the open-label period should be evaluated for MAS at Visit 1 of Treatment Period 2 on the same day; provided that measurement may be performed only once if the affected part to be evaluated is the same. Meanwhile, MAS needs to be evaluated again if the affected part to be evaluated is not the same.

- MAS measurement during the open-label period

During the open-label period, MAS should be evaluated for the flexors at which the muscle given the study treatment functions (fingers, thumb, wrist, elbow, fore-arm) (Table 6). If the subject is determined to be eligible, the V5/QRV and V1 would be on the same day, and therefore, the MAS measured at V5/QRV of the previous treatment period should not be measured again on V1; the measurement on V5/QRV should be used for the assessment (Figure 6). MAS on flexors to be newly

assessed on V1 should be evaluated before dose on V1. The MAS on the shoulder should be evaluated comprehensively for the adductor and inverter.

Table 6 Regions to be evaluated for MAS during the open-label period

| Number | Muscles to be injected | Regions to be evaluated for MAS |
|--------|--------------------------------|--|
| A1 | Biceps brachii | Elbow flexors (flexion) |
| A2 | Brachialis | |
| A3 | Brachioradialis | |
| B1 | Flexor carpi radialis | Wrist flexors (flexion) |
| B2 | Flexor carpi ulnaris | |
| C1 | Flexor digitorum profundus | Fingers (flexion) |
| C2 | Flexor digitorum superficialis | |
| C3 | Lumbricales interossei | |
| D1 | Flexor pollicis longus | Thumb (flexion, adduction and opposition) |
| D2 | Adductor pollicis | |
| D3 | Opponens pollicis | |
| E1 | Pronator teres | Forearm (pronate) |
| E2 | Pronator quadratus | |
| F1 | Teres major | Shoulder (adduction and internal rotation) |
| F2 | Latissimus dorsi | |
| F3 | Pectoralis major | |
| F4 | Subscapularis | |

| Visit | SV | Part 1 | | | | | Part 2 | | | | | Part 3 | | | | | Part 4 | | | | | |
|------------|----|--------|----|----|----|----|--------|----|----|----|----|--------|----|----|----|----|--------|-----|----|----|----|---|
| | | V1 | V2 | V3 | V4 | V5 | V1 | V2 | V3 | V4 | V5 | V1 | V2 | V3 | V4 | V5 | V1 | V2 | V3 | V4 | V5 | |
| A.Elbow | ● | ● | ● | ● | ● | ● | (○) | ● | ● | ● | ● | (○) | ● | ● | ● | ● | (○) | ● | ● | ● | ● | ● |
| B.Wrist | ● | ● | ● | ● | ● | ● | | | | | | | ● | ● | ● | ● | ● | (○) | ● | ● | ● | ● |
| C.Finger | ● | ● | ● | ● | ● | ● | (○) | ● | ● | ● | ● | (○) | ● | ● | ● | ● | (○) | ● | ● | ● | ● | ● |
| D.Thumb | | ● | ● | ● | ● | ● | | | | | | | | | | | | | | | | |
| E.Forearm | | | | | | | ● | ● | ● | ● | ● | (○) | ● | ● | ● | ● | (○) | ● | ● | ● | ● | ● |
| F.Shoulder | | | | | | | ● | ● | ● | ● | ● | | | | | | ● | ● | ● | ● | ● | ● |

● : MAS measurement (before treatment)
 (○) : Use V5 or QRV MAS measurement

Figure 6 Subjects to be evaluated for MAS

9.1.1.2. Numeric Rating Scale (NRS)

According to "2. SCHEDULE OF ACTIVITIES (SoA)" the investigator (or subinvestigator) will use NRS (Figure 7) to evaluate the severity of flexors pain.

The investigator will perform the interview on NRS following the assessment of MAS. Each subject will be interviewed on the severity of pain on the treated part when extended based on a scale with 0 being "no pain" and 10 being "the worst imaginable pain"; 1 response on the scale should be selected by the subject.

| | | | | | | | | | | |
|---------|---|---|---|---|---|---|---|---|---|--------------------------------|
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| No pain | | | | | | | | | | Pain as bad as you can imagine |

Figure 7 Numeric Rating Scale (NRS) for pain

- NRS measurement during the blinded period

During the blinded period, the severity of pain in the elbow flexors will be evaluated.

- NRS measurement during the open-label period

During the open-label period, a major part with pain [specify 1 part from among fingers, thumb, wrist, elbow, fore-arm (pronate), and shoulder] will be evaluated for the severity of pain on Visit 1. The part to be evaluated does not have to be the same within each treatment period, but should be the same part as that evaluated for MAS.

9.1.1.3. Disability Assessment Scale (DAS)

According to "2. SCHEDULE OF ACTIVITIES (SoA)" the investigator (or subinvestigator) will use the 4 disability assessment parameters presented in Table 7 and evaluate all of them based on the scale presented in Table 8. Before starting the study treatment, the investigator shall discuss with the subject, and select and evaluate 1 parameter agreed with the subject as the "main assessment parameter." The assessor should in principle remain unchanged throughout the study period. The main assessment parameter should also remain unchanged throughout the study period.

Table 7 Disability assessment parameters

| | Content of assessment |
|--------------|--|
| Hygiene | The extent of maceration/ulceration and/or palmar infection, palm/hand cleanliness, ease of cleanliness, ease of nail trimming, and interference with hygiene-related disability in the subject's daily life |
| Pain | The intensity of pain/discomfort, and the interference that upper-limb pain-related disability has in the patient's daily life. |
| Dressing | The difficulty or ease for the subject in putting on the relevant clothing (e.g., shirts, jackets, gloves, etc.) and the interference that upper-limb dressing-related disability has in the patient's daily life. |
| Limb posture | The psychological and/or social interference that the disfigured upper limb has in the patient's daily life. |

Table 8 Disability Assessment Scale

| | Description |
|-----------------------------|--|
| 0: No functional disability | No functional disability |
| 1: Mild disability | Noticeable but does not interfere significantly with normal activities |
| 2: Moderate disability | Normal activities require increased effort and/or assistance. |
| 3: Severe disability | Normal activities limited. |

9.1.1.4. Clinical Global Impression of Change (CGI) assessed by a investigator

The investigator (or subinvestigator) will evaluate CGI according to "2. SCHEDULE OF ACTIVITIES (SoA)"; Changes in spasticity (Clinical Global Impression) from baseline (V1 in each treatment phase) will be evaluated by 9 grades as shown in Table 9.

The investigator shall also consider the subject's clinical symptoms and adverse events pertinent to the assessment of CGI. Also, the therapeutic effect of the product injected in the subject's fingers, wrist, and elbow should be taken into an account. The assessor should in principle remain unchanged throughout the study period.

Table 9 Clinical Global Impression of Change (CGI)

| | |
|----|---------------------|
| -4 | Very much worsened |
| -3 | Much worsened |
| -2 | Moderately worsened |
| -1 | Slightly worsened |
| 0 | Unchanged |
| +1 | Slightly improved |
| +2 | Moderately improved |
| +3 | Much improved |
| +4 | Very much improved |

9.1.1.5. Clinical Global Impression of Change (CGI) assessed by a patient

According to "2. SCHEDULE OF ACTIVITIES (SoA)" the investigator (or subinvestigator) will use Table 9 to record subject-reported CGI. The investigator shall interview each subject on changes in spasticity from predose, and the subject will evaluate it using Table 9.

9.1.1.6. Time to patient-reported onset of spasticity symptom relief (Visit 2):

According to "2. SCHEDULE OF ACTIVITIES (SoA)" the investigator (or subinvestigator) will record the time to alleviation of spasticity reported by subjects. The investigator shall ask the subject whether the product was effective on the spasticity, and if the subject's response to the question is positive, ask him/her "how many days did it take for the therapeutic effect to appear after the current dose?" and record the number of days.

9.1.1.1. Patient-reported benefit of injection (Visits 3, 4, and 5)

According to "2. SCHEDULE OF ACTIVITIES (SoA)" the investigator (or subinvestigator) will record the efficacy of treatment reported by subjects. The investigator shall ask, "Was the product effective?" and the subject shall respond either by "Yes" or "No."

9.2. Adverse events

Definitions of adverse events and serious adverse events (SAE) are as specified in Appendix 4. The investigator or a person assigned by the investigator is responsible for detecting, recording, and reporting events that match the definitions of adverse events and SAEs, and also, responsible for follow-up investigations on SAEs, as well as events related to the study drug or this study, and events that resulted in treatment discontinuation or subject withdrawal (See section 8).

9.2.1. Period subject to collection of data related to adverse events and SAEs, and the frequency of such data collection

- All SAEs will be collected from the start of treatment until Final Visit at the time points specified in the SoA (Section 2).
- All AEs will be collected from the start of treatment until Final Visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4 . The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4 .

9.2.2. Method used to detect adverse events and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.2.3. Follow up on adverse events and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory requirements of SAE reporting

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Cardiovascular events and death

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

9.2.6. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study treatment and until Final Visit.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix [X].
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.3. Management of overdose

A dosage of the product exceeding 400 units within 24 hours shall be considered as overdose in this study. Overdose may cause excessive pharmacodynamic responses such as hyposthenia, muscular paralysis, and other localized adverse reactions. Symptoms and signs may not immediately appear following dose. Moreover, blepharoptosis, dysarthria, dysphagia, dyspnea, myasthenia, and other events suspected to be an effect on other muscles distal to the treated muscle have been reported overseas. If such a symptom appears, the subject should be carefully monitored, and given appropriate interventions, if necessary with hospitalization. Also, supportive therapies such as artificial breathing should be considered for respiratory symptoms.

Upon confirmation of overdose, the investigator should;

1. Contact the Medical Monitor immediately.

Carefully monitor the adverse event/SAE, and laboratory abnormalities in the subject for at least 4 weeks; and

Document the quantity of the excess dose as well as the duration of the overdosing in the CRF..

The investigator shall discuss with the sponsor's medical monitor on the clinical assessment of the subject, and upon which, decide whether or not to discontinue the study treatment.

9.4. Safety assessments

Assessment timepoints for all safety parameters are as shown in SoA.

9.4.1. Physical examination

Physical examination (complete version): Only during screening

- The head and neck, skin, lungs, cardiovascular system, abdominal region (liver and spleen), gastrointestinal system, lymph node, and nervous system should be examined, and the results thereof should be recorded; these organs should be examined for the presence/absence of pre-existing conditions and abnormal findings, and if there is any suspected abnormality, detailed examinations should be performed.
- The pulmonary function test should be conducted in details if any sign of pulmonary impairment is found. For the pulmonary function test, spirometry by pulmonologists is recommended.

Physical examination (simplified version): To be conducted only if an eligibility criterion is not met during the open-label period.

- At least, the lungs, cardiovascular system, and abdominal region (liver and spleen) should be examined, and the results thereof should be recorded.
- The investigator should pay attention to clinical signs and symptoms related to a history of serious disease.

The physical examinations should be performed by doctors in accordance with the standard clinical guidelines of each study site.

9.4.2. Vital signs

- For the vital signs, body temperatures (oral, intra-aural, or axillary fossa), systolic/diastolic blood pressures, and pulse rates should be measured in a semi-recumbent position after a 5-minute rest.
- If a temperature is to be measured orally, the subject must refrain from eating food or drinking beverage within 5 minutes before the measurement. The method for the measurement of body temperature must remain the same throughout the study.
- The blood pressures and pulse rates should be measured with an automated device. A manual method may be used only if there is no automated device available for use.

9.4.3. Height and weight

The standard clinical guidelines of each study site should be followed.

9.4.4. Pulmonary test

- Refer to SoA for the timepoints and frequency of testing.

- If post-injection SpO₂ is decreased by 3% or more from the baseline, medical examination by pulmonologist is recommended.
- If a medical institution has no pulmonologist, visit other hospitals for medical examination by specialists. For the pulmonary function test, spirometry by pulmonologists is recommended.

9.4.5. ECG

- QTc should be determined based on a single measurement of ECG or the mean of ECG measured at 3 timepoints in a short period of time (e.g., 5 to 10 minutes).
- An automated measurement and manual re-interpretation in accordance with SoA should be used to collect data on the heart rates, PR, QRS, QT, and QTc interval. Refer to section [8.2.2.](#) for QTc-related treatment discontinuation standard, and additional QTc to be measured as required.
- Each interval between timepoints for the measurement of ECG should be minimized as much possible (within 2 minutes). The measurement of ECG should be performed 3 times consecutively and completed within 5 to 10 minutes.

9.4.6. Neutralizing antibody test

The investigator shall draw blood for neutralizing antibody samples in accordance with the study schedule. The neutralizing antibody will be measured collectively by a central laboratories designated by GSK (Intertek Pharmaceutical Services Co. and Pacific BioLabs Co.). The screening samples will be retained temporarily by the central laboratories, and then, upon retrieval of samples from all subjects, will be collected and tested by Intertek for screening. Samples tested positive at Intertek will be separately sent to Pacific BioLabs for retest to finalize the results of neutralizing antibody test. The above procedures shall also be taken for samples collected for Week 12 visit during the blinded period, and upon completion of study treatment in all subjects.

9.4.7. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory parameters that should be tested, and to SoA for the timepoints and frequency of testing.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If a result of clinical laboratory test not scheduled in the protocol is obtained by a study site, which requires a change in the patient management, or is determined to be clinically important by the investigator, that is SAE, adverse event, an event requiring dose modification, or any other relevant event, the record thereof must be documented in the CRF.
- Follow-up investigation may be performed at any time during the study as determined to be necessary by the investigator, or required by the Japanese regulation.

9.5. Pharmacokinetics

PK parameters are not evaluated in this study.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics/Pharmacogenetics

Genetics and pharmacogenetics are not evaluated in this study.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

9.9. Pharmacoeconomics

Pharmacoeconomic parameters are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

This study is not intended to verify a statistical hypothesis, but is rather intended to verify that the responder rate in the 400 units group exceeds that in the 240 units group, and for which, about 120 subjects (60 in each treatment group) are to be enrolled.

During Treatment Period 1 of this study, 160 units of the product will be administered in the muscle which affects the elbow; thus, the sample size was determined in reference to an overseas phase III study (Study 127) in which a similar dosage as this study (150 units) was administered in the muscle which affects the elbow. The responder rate in the elbow at Week 6 of the initial dose in Study 127 was 72.2% and 47.1% in the product 300 units group (150 units in the muscle which affects the elbow flexors) and placebo group, respectively. The number of subjects in the intention-to-treat (ITT) population was small in both the product 300 units group and placebo group of Study 127, which was 18 subjects each; thus, considering the uncertainty of the results of Study 127, the responder rates in the product 400 units and 240 units groups in this study were conservatively assumed to be 70.0% and 50.0%, respectively. Assuming that the sample size is 60 subjects in each group, the power of test to detect an intergroup difference in the responder rates would be about 62% with a two-sided significance level of 5% while the probability of the responder rate in the product 400 units group to exceed that in the product 240 units group as a point-estimate would be $\geq 98\%$.

With about 120 subjects enrolled, 100 subjects are expected to complete Week 48 of the initial dose.

10.2. Populations for Analyses

Populations for statistical analyses in this study are defined as follows.

| Population | Description |
|------------|--|
| ITT | All subjects randomized in the study and had at least 1 post-baseline efficacy assessment: ITT is the primary efficacy analysis population, and the subjects will be analyzed in line with the randomized treatment group. |
| Safety | All subjects randomized in the study and received study treatment at least once: The subjects will be analyzed based on the treatment actually given. |

10.3. Statistical Analyses

10.3.1. Efficacy Analyses

This study is not intended to verify a statistical hypothesis; thus, there will be no statistical test.

All of the efficacy analyses will be performed on the ITT population separately for the blinded period and the open-label period.

| Endpoints | Statistical Analysis Methods |
|-------------|---|
| Primary | <p>The primary endpoint is the proportion of subjects whose MAS score on the elbow at Week 6 of the initial dose decreased by at least 1 level from the baseline (responder rate). The primary endpoint will be calculated as the proportion of subjects whose MAS score decreased by at least 1 level from the baseline in the ITT population. Also, a 95% confidence interval of the intergroup difference in the responder rate will be computed. Subjects with no MAS score available at Week 6 will not be counted as subjects whose MAS score decreased by at least 1 level from the baseline (that is, counted in as non-responder).</p> <p>The MAS scores, 0, 1, 1+, 2, 3, and 4 will be encoded to 0, 1, 2, 3, 4, and 5, respectively, for the analysis purpose.</p> |
| Secondary | <p>Unless specified otherwise, the data up to Week 12 of treatment will be summarized for each repeated dose during the open-label period.</p> <p>During the blinded period, a mixed model for repeated measurement (MMRM) will be used for the analysis on the endpoints specified below, and the least-square mean and 95% confidence interval will be calculated. The details of the model will be described in the statistical analysis plan. For the open-label period, only a summary statistics will be performed for each treatment group. Missing values will not be imputed.</p> <ul style="list-style-type: none"> · Change in MAS score in the fingers, thumb, wrist, and elbow from the baseline · Change in Disability Assessment Scale (primary endpoint) from the baseline <p>The proportion of subjects in whom MAS score in the fingers, thumb, wrist, and elbow decreased by at least 1 level from the baseline (responder rate) during the blinded period will be analyzed with the same method as that for the primary endpoint. For the open-label period, the denominator to be used for the calculation of responder rate shall be the number of subjects in each subgroup stratified by the number of injections given, not the ITT population. Also, a 95% confidence interval of the intergroup difference in the responder rate will not be calculated.</p> |
| Exploratory | <p>Time to patient-reported onset of spasticity symptom relief will be evaluated for subjects who reported alleviation of spasticity at in 2 weeks postdose. The number of days from dose to the alleviation of spasticity will be summarized for each treatment group.</p> <p>Clinical Global Impression of Change (CGI) assessed by a investigator, CGI assessed by a patient, and Patient-reported benefit of injection will be summarized for each treatment group. Missing values will not be complemented.</p> <p>Other details will be specified in the statistical analysis plan.</p> |

10.3.2. Safety Analysis

Safety analyses will all be performed on the safety population separately for the blinded and open-label periods.

| Endpoints | Statistical Analysis Method |
|-------------|--|
| Primary | Not applicable |
| Secondary | Adverse events that occurred in the overall study period, blinded period, and open-label period will be summarized for each treatment group. For the blinded period, 2 patterns of analyses on adverse events will be performed; one is on adverse events that occurred between the initial dose and the first dose in the open-label period (or at the completion of study if no dose is given in the open-label period or at the study withdrawal), and another one is on adverse events that occurred within 84 days from the initial dose. Adverse events will be summarized separately for SOC (system organ class) and PT (preferred term). Also, adverse events related to study treatment, adverse events that resulted indiscontinuation, adverse events by subgroups stratified by severity, and serious adverse events will be summarized. Laboratory findings and vital signs at each visit and their changes from baseline will be summarized for each treatment group. |
| Exploratory | Will be specified in the statistical analysis plan. |

10.3.3. Other analyses

Other analyses will be specified in the statistical analysis plan.

10.3.4. Interim analyses

The details of the interim analysis plan will be specified in the statistical analysis plan.

When all subjects (except for early termination) complete the visit at Week 24 of the initial dose, the data on all of the subjects until Week 24 of the initial dose may be locked, unblinded, and analyzed for reporting to authorities.

11. Reference

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12. Appendices

12.1. Appendix 1: Abbreviations and trademarks

Trademark

| Trademark of Glaxo Smithcline Group | Trademarks that do not belong to Glaxo Smithcline Group |
|-------------------------------------|---|
| Botox | — |

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in [Table 10](#) will be performed by central laboratory.
- A test needs to be performed by study sites only if the result cannot be obtained from the central laboratory in time for study treatment and/or assessment. Even if measurement is performed at a study site, another sample at the same assessment timepoint is separately required for measurement at central laboratory. If a result of measurement at the study site is to be used for a decision of study treatment and/or assessment, the result should be recorded in the CRF.
- Protocol-specific inclusion/exclusion criteria are as specified in section 6 of the protocol.
- Protocol-specific inclusion/exclusion criteria are as specified in section 6 of the protocol.

Table 10 Protocol-Required Safety Laboratory Assessments

| Clinical laboratory | Parameters | | | |
|--|--|----------------------|--|---|
| Hematological tests | Platelet count | | Erythrocyte indices: | Percentage of white blood cell: Neutrophil Lymphocyte Monocyte Eosinophil Basophil |
| | RBC | | Mean corpuscular volume (MCV) | |
| | Hemoglobin | | Mean corpuscular hemoglobin (MCH) | |
| | Hematocrit | | Reticulocyte count (%) | |
| | White blood cell count | | | |
| Chemistry ¹ | Urea nitrogen (BUN) | Potassium | Aspartate aminotransferase (AST) / Serum glutamic oxaloacetic transaminase (SGOT) ¹ | Total bilirubin and direct bilirubin |
| | Creatinine | Sodium | Alanine aminotransferase (ALT) / Serum glutamic pyruvic transaminase (SGPT) ¹ | Total protein |
| | Calcium | Alkaline phosphatase | | |
| Urinalysis | Specific gravity PH with test paper, glucose, protein, occult blood, ketone, bilirubin, urobilinogen, nitrite, and white blood cell esterase Microscopy (if occult blood or protein is deviated) | | | |
| Other tests | <ul style="list-style-type: none"> Pregnancy test (if necessary in a woman of child-bearing potential): Serum or urine human chorionic gonadotropin (hCG)² <p>The following parameters should be tested during the screening period.</p> <ul style="list-style-type: none"> Serological verification: HIV antibody The following parameters should be tested only for subjects with chronic hepatitis B or C that is stabilized at screening, and subjects currently receiving or expected to receive immunosuppressant. <ul style="list-style-type: none"> Serological verification: Hepatitis B virus surface antigen (HBsAg), and hepatitis C virus antibody The following parameter should be tested for women of no child-bearing potential. <ul style="list-style-type: none"> Follicle stimulating hormone and estradiol | | | |
| Caution: 1. Details of the discontinuation criteria based on hepatic function test, and the interventions and follow up necessary after the occurrence of hepatic events are specified in section 8.1 and Appendix 6. SAEs must be reported for all events with ALT IJYO3 times the upper limit of normal range (ULN), and at the same time, bilirubin IJYO2 times the ULN (direct bilirubin >35%), or ALT IJYO3 times the ULN, and at the same time, the international normalized ratio (INR) >1.5 if measured [which suggests a possibility of severe liver injury (applicable to Hy's Law)]. 2. Pregnancy tests should be performed with serum samples at screening, and with urine samples for routine tests after randomization. | | | | |

12.3. APPENDIX 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
 - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
 - Applicable ICH Good Clinical Practice (GCP) Guidelines
 - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
 - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
 - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
 - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Process of obtaining consent

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Data protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Composition of committee

No committee will be established.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- Disclosure of a Clinical Study Report (CSR) after the evaluation by the regulatory authority(ies).
- GSK may post the study information and tabulated-form study results on the website (www.ClinTrials.gov) of the U.S. National Institution of Health (NIH) or other websites open to the public
- GSK may post the study results to scientific journals that conduct peer review in order to report the study results.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the corresponding list of source documents.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.4. APPENDIX 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of an SAE

If an event does not correspond any of the above definitions of an AE, even if it is a serious condition, it will not be regarded as an SAE (e.g.; hospitalization due to the signs/symptoms of the disease being studied, death caused by exacerbation of the disease).

A SAE is defined as any untoward medical occurrence that, at any dose:**a. results in death****b. is life-threatening**

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. requires hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the investigator's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. is congenital anomaly/birth defect

f. other important medical situations:

- Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/angina unstable
- Cardiac failure congestive
- Arrhythmia
- Valvular disease
- Pulmonary hypertension
- Cerebrovascular event/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep vein thrombosis/pulmonary embolism
- Revascularisation

Recording of AEs and SAEs**AE and SAE Recording**

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and classify it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities - An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as “serious”, not when it is assessed as severe but when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of causality

- The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE.
- A “reasonable possibility” is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgement to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated.
- The investigator will also consult the IB, for marketed products, in the determination of his/her assessment.
- The investigator **must** record that he or she reviewed AEs and SAEs and assessed the causality in the medical record.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, prepare and send the follow-up report of SAE by amending the assessment result of the causality accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit all updated SAE data to GSK within 24 hours after obtaining the information.

Reporting of SAEs to GSK**SAE Reporting to GSK via Electronic Data Collection Tool**

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the SAE coordinator by telephone.
- Contacts for SAE reporting can be found in ATTACHMENT.

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE page of the CRF is the preferred method to transmit the information on SAEs to GSK.
- In rare circumstances and in the absence of facsimile equipment, initial notification by telephone is acceptable followed by a copy of the SAE page of the CRF sent by overnight mail or by courier.
- Initial notification via the telephone does not replace the need for the investigator (or subinvestigator) to complete and sign the SAE page of the CRF within the designated reporting time frames.
- The ATTACHMENT 1 shows a contact information to which the SAEs should be reported.

12.5. APPENDIX 5: Contraceptive Guidance and Collection of Pregnancy Information

Definition

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP

1. Premenarchal

Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

Postmenopausal women

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male study subject

- A male study subject who has a female partner of childbearing potential can participate in this study if he agrees to any of the following conditions:
- He must agree not to have a sex (sexual intercourse) with a person of the opposite sex as a normal favourable lifestyle (continuously having no sex for a long period of time) and also agree to keep that condition.
- If he has a sex with a woman of childbearing potential, he must agree to use a male condom and use at least one of the contraception methods with an annual failure rate below 1% which are shown in Table 11.
- A male study subject who has a pregnant or breastfeeding female partner must agree not to have a sex from the time during the study or use a male condom when having a sex.
- A male study subject must agree not to provide his sperm during the study.

Female study subject

A female study subject of childbearing potential can participate in this study if she agrees to use any of the extremely effective methods of contraception shown in Table 11 continuously and accurately. Among the methods of contraception shown in Table 11, those deleted with strikethrough lines have neither been approved nor been accepted in Japan.

Table 11 Extremely effective methods of contraception

| |
|--|
| User-dependent extremely effective methods of contraception ^a Their annual failure rates are below 1% if they are used continuously and accurately. |
| Contraception by mixed (estrogen and progestogen-containing) hormone preparation (inhibit ovulation) ^b <ul style="list-style-type: none"> • Oral • Intravaginal • Transdermal |
| Contraception by only progestogen-containing hormone preparation (inhibit ovulation) ^b <ul style="list-style-type: none"> • Injection |
| User-independent extremely effective methods of contraception |
| <ul style="list-style-type: none"> • Contraception by only progestogen-containing implantable hormone preparation (inhibit ovulation)^b • Intrauterine device (IUD) • Intrauterine system (IUS) • Bilateral tubal occlusion |
| Male partner's vasectomy (If her male partner has been vasectomised, it is an extremely effective method of contraception for a woman of childbearing potential if that partner is the only man with whom she has a sex and it has been confirmed that he is sterile. Otherwise, he/she must use other additional extremely effective method(s) of contraception.) |
| Having no sexual relations (If the subjects decides to refrain himself or herself from having a sex of the opposite sex for the entire period when there is a risk of the investigational product, abstinence is deemed to be an extremely effective method of contraception. However, the credibility of abstinence needs to be evaluated during the study period and from the perspectives of the subject's normal favourable lifestyle.) |

Notes:

- a. The usual failure rate is different from the rate when contraception is used continuously and accurately. The subjects should use the methods of contraception that match with regulations concerning the methods of contraception for study subjects in each country.
- b. The efficacy of contraception by hormone preparations may decrease as a result of the interaction with the investigational product. In that case, the subject should use two extremely effective methods of contraception during the treatment period and at least for 3 months after the last dose of the investigational product.

Pregnancy test

- A woman of childbearing potential can be enrolled to this study only if it is confirmed that she is negative in a highly sensitive serum pregnancy test along with her menstrual period.
- Pregnancy test should be performed if no menstruation occurred or she is suspected to be pregnant.
- Analysis should be performed according to the package insert using a testing kit provided by GSK.

Collection of pregnancy information**If a male study subject's partner becomes pregnant**

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

For a female study subject who discovers her pregnancy while participating in this study,

- The administration of the investigational product will be discontinued.

12.6. APPENDIX 6: Liver Safety Required Actions and Follow up Assessments

In order to secure the subject's safety and evaluate the causes of liver event, **the criteria for discontinuation and follow-up based on the liver function test values in the phase III-IV studies** will be stipulated.

Criteria for discontinuation based on the liver function test values in the phase III-IV studies and necessary follow-up

| Criteria for discontinuation based on the liver function test values | |
|---|--|
| ALT | ALT \geq 8xULN |
| ALT increase | ALT \geq 5xULN but <8xULN persists for \geq 2 weeks ALT \geq 3xULN but <5xULN persists for \geq 4 weeks |
| Bilirubin ^{1,2} | ALT \geq 3xULN and bilirubin \geq 2xULN (>35% direct bilirubin) |
| INR ² | ALT \geq 3xULN and INR>1.5, if INR measured |
| Cannot Monitor | ALT \geq 5xULN but <8xULN and cannot be monitored weekly for \geq 2 weeks ALT \geq 3xULN but <5xULN and cannot be monitored weekly for \geq 4 weeks |
| Symptom ³ | ALT \geq 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity |
| Necessary measures and assessment items for liver event | |
| Actions | Follow Up Assessments |
| <ul style="list-style-type: none"> Immediately discontinue the administration of the investigational product. Report it to GSK within 24 hours. Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE². Perform liver event follow up assessments Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below) Do not restart/rechallenge participant with study treatment unless allowed per protocol and GSK Medical Governance approval is granted If the resumption/re-administration of the investigational product is not stipulated in the protocol or approved by GSK's Medical Governance, the administration of the investigational product will be discontinued | <ul style="list-style-type: none"> Viral hepatitis serology⁴ Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend Only in those with underlying chronic Hepatitis B at study entry (identified by positive Hepatitis B surface antigen) quantitative Hepatitis B DNA and Hepatitis delta antibody⁵ Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). Fractionate bilirubin, if total bilirubin \geq 2xULN Obtain complete blood count with differential to assess eosinophilia Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. |

| | |
|--|--|
| <p>permanently and the follow-up prescribed in the protocol 8.1. will be conducted.</p> <p>MONITORING:</p> <p><u>For bilirubin or INR criteria:</u></p> <ul style="list-style-type: none"> Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline A specialist or hepatology consultation is recommended <p><u>For other criteria:</u></p> <ul style="list-style-type: none"> Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72 hrs Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline | <ul style="list-style-type: none"> Record alcohol use on the liver event alcohol intake case report form (CRF) page <p><u>For bilirubin or INR criteria:</u></p> <ul style="list-style-type: none"> Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms. |
|--|--|

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT $\geq 3xULN$ and bilirubin $\geq 2xULN$. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.

All events of ALT $\geq 3xULN$ and bilirubin $\geq 2xULN$ (>35% direct bilirubin) or ALT $\geq 3xULN$ and INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)

Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen (HbsAg) and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody

Criteria for follow-up with continued treatment based on the liver function test values in the phase III-IV studies

| Criteria for follow-up based on liver test function values – Liver events to be followed | |
|---|---|
| Criteria | Actions |
| <p>ALT \geq5xULN and <8xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 2 weeks.</p> <p>OR</p> <p>ALT \geq3xULN and <5xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks.</p> | <ul style="list-style-type: none"> • Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT \geq5xULN and <8xULN to \geq3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline. |

12.7. APPENDIX 7: COUNTRY SPECIFIC DESCRIPTIONS

12.7.1. Regulatory and Ethical Considerations

This study will be conducted in compliance with the “Good Clinical Practice (GCP)” (MHW Ordinance No. 28, March 27, 1997) and the “Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, etc. (PMD Act)”.

GSK will submit the CTN to the regulatory authorities in accordance with the PMD Act before concluding the study agreement with the medical institution

12.7.2. Obtaining of Informed Consent

Prior to participation in the study, the investigator should fully inform the potential subject and/or his or her legally acceptable representative of the study using the information document. In doing so, the investigator should provide the subject sufficient time and opportunity to inquire about details of the study and obtain the subject and/or his or her legally acceptable representative’s signature or printed name and seal and date of consent on the consent form. The subject may take the informed consent form home to review it. The person who provided the explanation and the clinical research coordinator who provided the supplementary explanation should also sign or affix his or her printed name and seal on the consent form and enter the date of signature. If an impartial witness is needed, he or she should also sign or affix his or her printed name and seal on the consent form and enter the date of witness. The investigator should attach the original of the above signed or affixed with printed name/seal and dated consent form (and information document) to the original medical record such as medical chart (in accordance with the rules for records retention, if any, at each medical institution), retain it, and give a copy to the subject and/or his or her legally acceptable representative.

12.7.3. Study Implementation Period

July 2017 – February 2019

12.7.4. Study Conduct Structure

The Attachment 1 shows the sponsor’s information. Also, the Attachment 2 shows a list of medical institutions and investigators.

TITLE PAGE

Protocol Title: A phase III study (a placebo controlled, randomized, double-blind comparative study and an open-label, uncontrolled study) to evaluate the efficacy and safety of GSK1358820 in patients with post-stroke upper limb spasticity

Protocol Number: 02

Short Title: A phase III study to evaluate the efficacy and safety of GSK1358820 in patients with post-stroke upper limb spasticity

Compound Number: GSK1358820

Sponsor

GlaxoSmithKline K.K. (GSK)

1-8-1 Akasaka, Minato-ku, Tokyo 107-0052 Japan

The person responsible for operation of the study: PPD Director of Development of Drugs for Neurological Diseases, Department of Development, Clinical Research Department

Medical Monitor Name and Contact Information are shown on SRM.

Regulatory Agency Identifying Number(s):NA

Approval Date: 6-OCT -2017

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Signature of the Sponsor:

PPD

Director of Development of Drugs For Neurological Diseases,
Department of Development, Clinical Research Department
GlaxoSmithKline K.K. (GSK)

Date

The IMMS document approved is as follows:

Unique ID :

System Version:

Effective Date:

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|-------------------|-------------|
| Document | Date |
| Amendment 2 | 6-OCT-2017 |
| Amendment 1 | 24-MAY-2017 |
| Original protocol | 4-APR-2017 |

Amendment 1 : 24-MAY-2017

Overall Rationale for the Amendment:01

The protocol was changed based on the regulatory inquiries by the Pharmaceuticals and Medical Devices Agency (PMDA).

Overall Rationale for the Amendment:01

| Section # and Name | Description of Change | Brief Rationale |
|--|---|--|
| 1. SYNOPSIS | Add pulmonary test and description adjustment | Requested by PMDA |
| 2. SCHEDULE OF ACTIVITIES (SoA) | Add pulmonary test and description adjustment | Requested by PMDA |
| 5.1.3.1. Eligibility Criteria for Injection in and after Part 2 | Add pulmonary test | Requested by PMDA |
| 6.1.1. Screening Phase (Day -28 to Day -1) | Add pulmonary test | Requested by PMDA |
| 6.2.2. Day 1 (Prior to injection) | Description adjustment | Establish consistency with section 7.7.2 |
| 6.4. Screen Failures | Description adjustment | Not shown due to minor changes |
| 7.7.2. Contraindicated Medications/Therapies | Description adjustment | Establish consistency with section 6.2.2 |
| 9.1.1.4. Clinical Global Impression of Change (CGI) assessed by a investigator | Error correction | Not shown due to minor changes |
| 9.4.4. Pulmonary test | Add pulmonary test | Requested by PMDA |
| 9.4.5.ECG | Description adjustment | Add manual re-interpretation |

Amendment 2 : 6-OCT-2017

Overall Rationale for the Amendment: 02

The protocol was changed on the basis of the regulatory inquiries by the Pharmaceuticals and Medical Devices Agency (PMDA).

Overall Rationale for the Amendment: 02

| Section # and Name | Description of Change | Brief Rationale |
|---|---|--|
| Cover | Change of address | Office relocation |
| 1. SYNOPSIS, | Delete laboratory data from the Eligibility Criteria for Injection in and after Part 2. Add eligibility criteria regarding the pulmonary test. | GSK1358820 is unlikely to affect laboratory test data. Specify the acceptable range of SpO ₂ values. |
| 2. SCHEDULE OF ACTIVITIES (SoA) | Add a footnote. | Clarify the procedure for V1 assessment in and after Part 2. |
| 5.1.3.1. Eligibility Criteria for Injection in and after Part 2 | Delete laboratory data from the Eligibility Criteria for Injection in and after Part 2. Add eligibility criteria regarding the pulmonary test. | GSK1358820 is unlikely to affect laboratory test data. Specify the acceptable range of SpO ₂ values. |
| 6.2.2. Day 1 (Prior to injection) | Add eligibility criteria regarding the pulmonary test. | Specify the acceptable range of SpO ₂ values to ensure the safety. |
| 7.1. Treatments Administered Table 2. Muscle Involvement and Dose in the Blind Phase Table 3. Muscle Involvement and Reference Dose in the Open-Label Phase | Description adjustment | Not shown due to minor changes. |
| 7.7.1. Permitted Concomitant Drugs/Therapies | Description adjustment | Delete tolperisone hydrochloride, which has been withdrawn from the market. |
| 7.7.1. Permitted Concomitant Drugs/Therapies | Add a description regarding rehabilitation therapies. | Specify acceptable rehabilitation therapies and the procedure for collecting rehabilitation therapy related information. |
| 9.1.1.1. Modified Ashworth Scale (MAS) | Description adjustment | Add a description regarding MAS assessment on the thumb. |
| 9.1.1.1. Modified Ashworth Scale (MAS) Table 6. Regions to be evaluated for MAS during the open-label period | Description adjustment | Not shown due to minor changes |
| 9.4.2. Vital signs | Add a description regarding measurement in a sitting position. | Add an instruction for vital sign measurement. |
| 9.4.4. Pulmonary | Add a description regarding the | Specify the acceptable range of SpO ₂ values to |

| Section # and Name | Description of Change | Brief Rationale |
|---------------------------|------------------------------|------------------------|
| Test | pulmonary test. | ensure the safety. |

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12.8. APPENDIX 8: PROTOCOL AMENDMENT SUMMARY OF CHANGES

TABLE79

1. SYNOPSIS

Protocol Title: A phase III study (a placebo controlled, randomized, double-blind comparative study and an open-label, uncontrolled study) to evaluate the efficacy and safety of GSK1358820 in patients with post-stroke upper limb spasticity

Short Title: A phase III study to evaluate the efficacy and safety of GSK1358820 in patients with post-stroke upper limb spasticity

Rationale:

GSK1358820, botulinum toxin type A (hereafter referred as the product), is sterile, purified type A botulinum neurotoxin complex. Intramuscularly injected botulinum neurotoxin shows muscle relaxant effects by blocking the neuromuscular junction and inhibiting release of acetylcholine, a neurotransmitter. Since the approval of the product for strabismus and blepharospasm in US in 1989, the product is licensed for the treatment of various diseases, which respond to the muscle relaxant effects in more than 90 countries (as of Apr 2017).

In Japan, the product is licensed with 8 indications as an ethical drug so far: blepharospasm as a first indication in Oct 1996, followed by “hemifacial spasm” in Jan 2000, “spasmodic torticollis” in Jun 2001, “talipes equinus associated with lower limb spasticity in pediatric patients two years of age and older with cerebral palsy” in Feb 2009, “upper limb spasticity” and “lower limb spasticity” in Oct 2010, “severe primary maschalephidrosis” in Nov 2012, and “strabismus” in Jun 2015. For “upper limb spasticity,” 240 units of the product is approved as a maximum dose per administration. In US, as a maximum dose per administration, 400 units of injection of the product have been approved for the treatment of upper limb spasticity in adult patients in 2015; therefore, the authorized dose of the product between US and Japan is different.

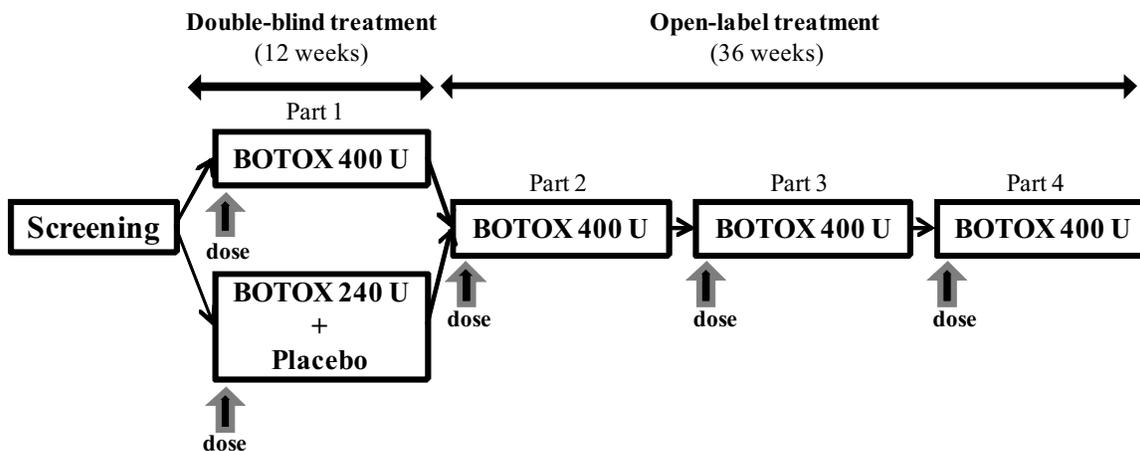
This study is a multicenter, double blind, placebo controlled phase III domestic study and aims to evaluate the efficacy and safety of 400 units of the product in patents with post-stroke upper limb spasticity. The study was planned to increase the maximum dose per administration in Japan to 400 units from 240 because the treatment with 240 units of the product, a maximum dose per administration, is considered to be insufficient in some patients with post-stroke upper limb spasticity.

Objectives and Endpoints:

| Objectives | Endpoint(s) |
|---|---|
| Primary | |
| To evaluate the efficacy of the injections of 400 units of the product at Week 6 (finger/ wrist flexors: 240 units, elbow flexors: 160 units), comparing to that of 240 units (finger/ wrist flexors: 240 units, elbow flexors: placebo). | The responder rate: The rate of the subjects that Modified Ashworth Scale (MAS) score was reduced at least 1 from baseline in the elbow flexors. |
| Secondary | |
| To evaluate the efficacy of 400 units of the product, comparing to 240 units of the product | <ul style="list-style-type: none"> • The responder rate of MAS score from baseline in the finger, thumb and wrist flexors • Changes in MAS score from baseline in the finger, thumb, wrist and elbow flexors • Changes in Disability Assessment Scale (DAS) from baseline |
| To evaluate the safety and tolerability of the product of 400 units, comparing to 240 units of the product/ To evaluate the safety and tolerability of 400 units of the product | <ul style="list-style-type: none"> • Adverse events • Physical examinations • Clinical laboratory tests (haematology, blood biochemistry, urinalysis) • Vital signs (heart rate, blood pressure, body temperature) |
| Exploratory | |
| To evaluate the efficacy of 400 units of the product | <ul style="list-style-type: none"> • Changes in MAS score from baseline in finger, thumb, wrist, elbow, pronation of the forearm and shoulder flexors |
| To evaluate the other efficacy of the product of 400 units, comparing to 240 units of the product/ To evaluate the other efficacy of 400 units of the product | <ul style="list-style-type: none"> • Changes in Numeric Rating Scale (NRS) for pain from baseline • Changes in other items of DAS from baseline • Clinical Global Impression of Change (CGI) of functional disability by an investigator • CGI of functional disability by a patient • Time to patient-reported onset of spasticity symptom relief • Patient-reported benefit of injection • Time to qualification for retreatment |
| To evaluate neutralizing antibody production | <ul style="list-style-type: none"> • Testing for neutralizing antibody |

Overall Design:

This study is a 48-week multicenter, phase III study (a placebo controlled, randomized, double-blind comparative study and an open-label, uncontrolled study) to evaluate the efficacy and safety of the product in patients with post-stroke upper limb spasticity. The study period is up to 52 weeks, consisting of a screening phase up to 4 weeks, minimum 12-week blind phase (Part 1), maximum 36-week open-label phase (12 weeks per cycle with maximum 3 treatment phases: Part 2, Part 3 and Part 4).

**Number of Participants:**

Approximately 120 subjects (approximately 60 in each group) will be randomized to obtain an evaluable subject sample of approximately 100 at Week 48 as subjects with completion of the study.

Treatment Groups and Duration:**Screening Phase (Day -28~Day -1)**

Evaluation and screening tests will be performed 28 to 7 days (± 3 days) before initial injection (Day 1) as a starting point. The investigator will decide which arm to be injected during screening phase.

Blind Phase (minimum 12 Weeks): Placebo Controlled, Randomized, Double Blind Design

Subjects who meet the inclusion criteria will be randomly assigned 1:1 to either the 400 or the 240 units group.

- In the 400 units group, a total of 240 units of the product will be injected into the muscles that act on the finger (including thumb flexors) and wrist flexors, and a total of 160 units into the muscles that act on the elbow flexors; a total of 400 units of the product will be injected.
- In the 240 units group, a total of 240 units of the product will be injected into the muscles that act on the finger (including thumb flexors) and wrist flexors. Placebo will be injected into the muscles that act on the elbow flexors. A total of 240 units of the product will be injected.

If the total dose for the muscles that act on the finger and wrists flexors is ensured by 240 units, and 160 units for the muscles that act on the elbow flexors, the dose can be adjusted at an investigator's discretion based on the subject's symptoms.

Open-Label Phase (maximum 36 Weeks): Uncontrolled, Open-Label Design

The product of 400 units will be injected in both groups. The product can be injected up to 3 times after completion of Part 1 in the blind phase. In the open-label phase, subjects whom the investigator considers eligible for the injections will be treated. The next injections cannot be performed until the eligibility of the subject has been confirmed by the investigator.

In the open-label phase, the muscle to be injected and the dose will be decided by the investigator on the basis of the patient's symptoms, and a total dose of 400 units of the product will be injected in a divided dose. For the muscles that the investigator considers unnecessary to be treated, an injection may be skipped. The involving muscle and the dose do not have to be same each time always.

Eligibility Criteria for Injection in and after Part 2

In the open-label phase (Part 2, Part 3, and Part 4), only the subjects whom the investigator considers eligible for the study will be injected. The eligibility is evaluated at a study visit after Week 12 (V5. If a subject does not meet the criteria at V5, the eligibility is evaluated at QRV (Qualification for Retreatment Visit). Subjects are considered to be eligible if the following criteria are all satisfied:

- 1) At least 12 weeks (84 days) have passed since the preceding dose
- 2) Among the finger, wrist or elbow flexors, 2 flexors have at least 2 on the MAS (except only the finger and wrist flexors of 2 on the MAS)
- 3) Subject who request the injections
- 4) Subjects whom an investigator considers an injection of 400 units of the product is appropriate
- 5) Subjects who have not experienced serious adverse events (SAE) associated with the injections of the product

If subjects meet the criteria of the above 1) to 5) at V5 or QRV, body weight measurement, ECG, pulmonary function test, and pregnancy test will be performed to evaluate the following items. If subjects meet the following 6) to 8), the subjects will move forward to V1.

- 6) Body weight ≥ 40 kg
 - 7) Subjects who the investigator considers there are no unacceptable safety concerns [potential for serious adverse events, electrocardiogram (ECG) or abnormal pulmonary function value*] due to 400 U of BOTOX
- * This study will use SpO₂ (oxygen saturation) as a parameter of pulmonary function. A subject who has a $\geq 3\%$ reduction from the pre-injection SpO₂ (Day 1) in post-injection SpO₂ or whose SpO₂ value is $< 95\%$ should be referred to a pulmonologist. A subject with pulmonary dysfunction due to study treatment also should be referred to a pulmonologist. If the subject is considered by the pulmonologist to have no concerns about pulmonary function, the investigator should carefully consider whether to start the study treatment.
- 8) Women of childbearing potential who have negative pregnancy test result in urine

A pulmonary function test must be performed at V5 even if subjects do not meet the above 1) to 5) in accordance with the study operation schedule (SoA).

2. SCHEDULE OF ACTIVITIES (SoA)

Compliance with the protocol (including the list of the study conduct schedule) is important and required to conduct the study. Therefore, exemption or discharge cannot be allowed, except but emergency safety concerns arise.

The study operation schedule is shown on [Table 1](#). Examples of injections in the open-label phase based on evaluation of eligibility for injection are shown on [Figure 1](#), [Figure 2](#), [Figure 3](#), and [Figure 4](#).

Table 1 SCHEDULE OF ACTIVITIES (SoA)

| Visit | Screening ^a SV | Blind phase If a subject meets the eligibility at V5/ QRV, the subject will move forward to the open-label phase | | | | | | Open-label phase If a subject meets the eligibility at V5/QRV, the subject will move forward to the next treatment phase | | | | | | Completion visit Final Visit |
|---|------------------------------|---|----|----|----|--|--------------------------------------|---|----|----|----|--|--------------------------------------|---------------------------------|
| | | Part 1 | | | | | Eligibility evaluation ^b | Part 2/Part 3/ Part 4 | | | | | Eligibility evaluation ^b | |
| | | V1 (Day 1) | V2 | V3 | V4 | V5 ^c (Eligibility evaluation) | QRV | V1 | V2 | V3 | V4 | V5 ^d (Eligibility evaluation) | QRV | |
| Time from initial injection (Day 1) (Weeks) | — | 0 | 2 | 4 | 6 | 12 | Allowable Week 16 to 36 ^e | — | — | — | — | — | Allowable Week 24 to 36 ^e | 48/ Withdrawal |
| Time from injection day in each treatment phase (Weeks) | — | 0 | 2 | 4 | 6 | 12 | 16/ 20/ 24/ 28/ 32/ 36 | 0 | 2 | 4 | 6 | 12 | 16/ 20/ 24 | - |
| Acceptable visit windows (days) | — | ±4 | ±4 | ±4 | ±4 | +4 ^f | ±14 ^g | (+4) ^v | ±4 | ±4 | ±4 | +4 ^f | ±14 ^g | ±4 |
| Written informed consent | X ^h | | | | | | | | | | | | | |
| Randomization | | X ⁱ | | | | | | | | | | | | |
| Injections | | X | | | | | | X | | | | | | |
| Evaluation of eligibility | | | | | | X | X | | | | | X | X | |
| Inclusion/exclusion criteria ^j | X | X ⁱ | | | | | | | | | | | | |
| Subject demography | X | | | | | | | | | | | | | |
| MAS ^k | X | X ⁱ | X | X | X | X | X | X ^{l,t} | X | X | X | X | X | X |
| NRS ^l | | X ⁱ | X | X | X | X | X | X ^{l,t} | X | X | X | X | X | (X) ^r |
| DAS | | X ⁱ | X | X | X | X | X | X ^{l,t} | X | X | X | X | X | (X) ^r |
| CGI by a investigator | | | X | X | X | X | X | | X | X | X | X | X | (X) ^r |
| CGI by a patient | | | X | X | X | X | X | | X | X | X | X | X | (X) ^r |
| Time to patient-reported onset of spasticity symptom relief | | | X | | | | | | X | | | | | |
| Patient-reported benefit of injection | | | | X | X | X | X | | | X | X | X | X | (X) ^r |
| Physical examination (complete version) | X | | | | | | | | | | | | | |
| Physical examination (simplified version) | | X ⁱ | | | | X | | X ^{l,t} | | | | X | | X |
| Medical history | X | X ⁱ | | | | | | | | | | | | |
| Vital signs ^m | X | X ⁱ | | | | X | | X ^{l,t} | | | | X | | X |
| Height | X | | | | | | | | | | | | | |
| Body weight | X | | | | | X ^u | X ^u | | | | | X ^u | X ^u | |
| Pulmonary function test | X | X | | | | X | X ^u | | | | | X | X ^u | X |
| Electrocardiogram | X | | | | | X ^u | X ^u | | | | | X ^u | X ^u | |
| Pregnancy test ⁿ | X | X ⁱ | | | | X ^u | X ^u | | | | | X ^{s,u} | X ^u | X |
| Laboratory test ^o | X | | | | | X | | | | | | X | | X |
| Adverse events ^p | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications/therapies | X | X ⁱ | X | X | X | X | X | X | X | X | X | X | X | X |

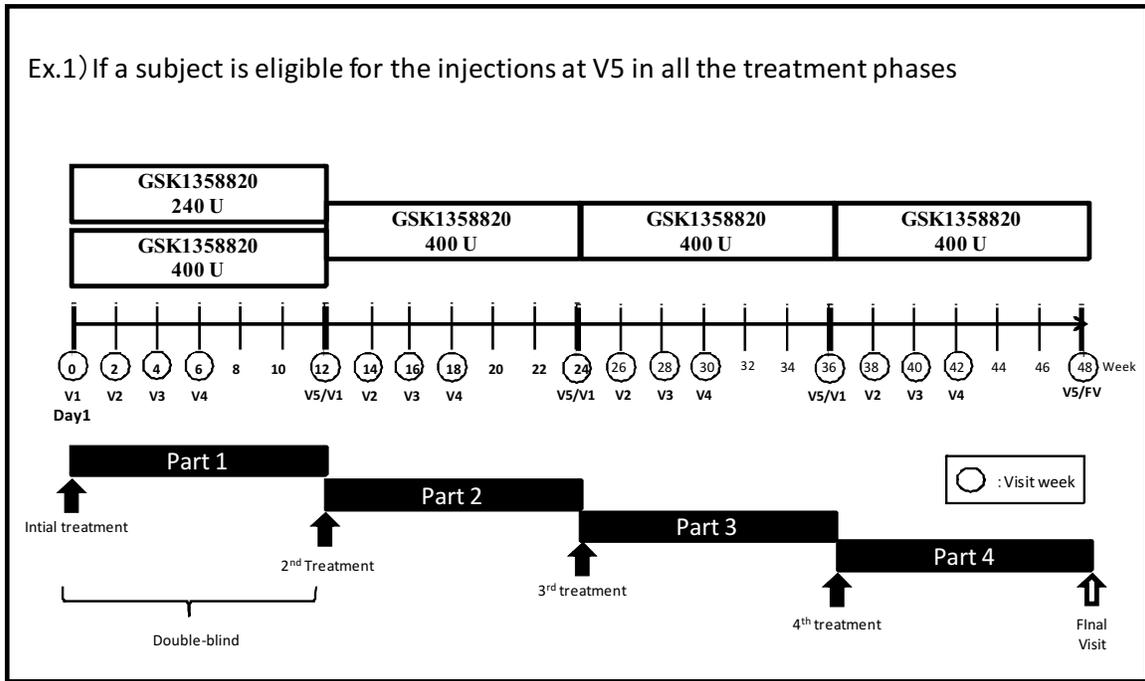


Figure 1 Eligibility Evaluation in the Open-Label Phase (Example 1)

If a subject is eligible for the injections at V5 in all the treatment phases, 4 injections will be performed throughout the study. Week 48 visit is performed also as a completion visit.

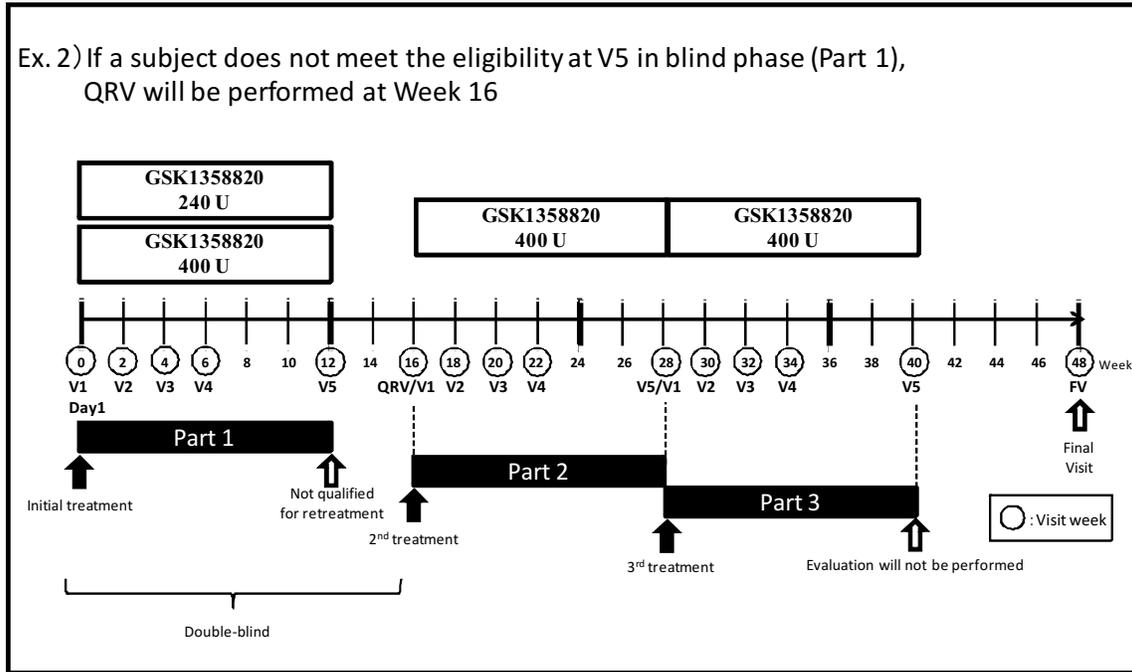


Figure 2 Eligibility Evaluation in the Open-Label Phase (Example 2)

If a subject does not meet the eligibility at V5 in blind phase (Part 1), QRV will be performed at Week 16. V5 in Part 3 is at Week 40; therefore, eligibility evaluation will not be performed. After V5 at Week 40, FV will be performed at Week 48.

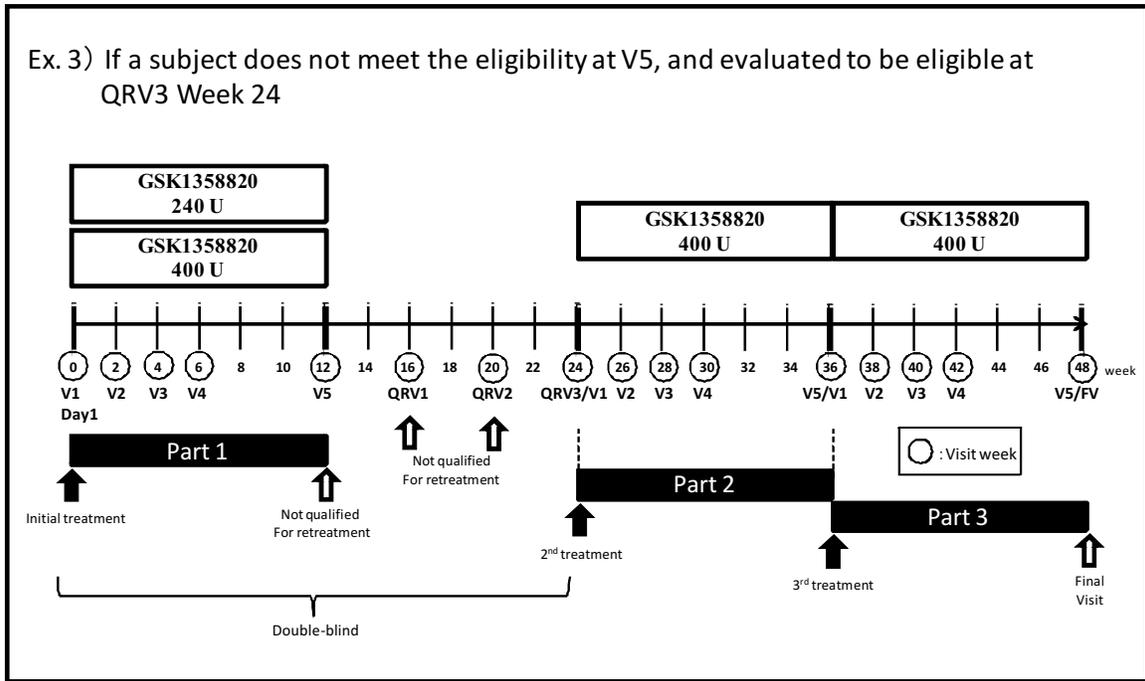


Figure 3 Eligibility Evaluation in the Open-Label Phase (Example 3)

If a subject does not meet the eligibility at V5 in the blind phase (Part 1), QRV will be performed until the eligibility have confirmed at 4 weeks intervals, at V5 as a starting point. If a subject is evaluated to be eligible at QRV3 Week 24, the injections in Part 2 will be performed on the same day as QRV3. V5 in Part 3 is in Week 48, therefore, at V5, completion visit (FV) will be also performed.

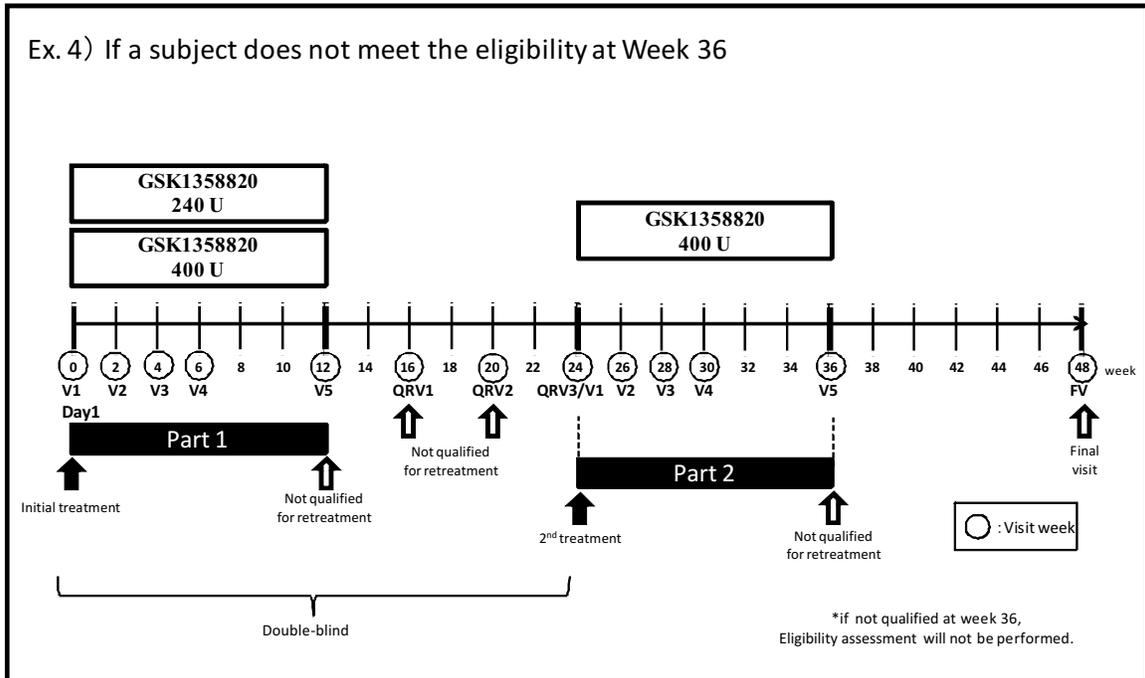


Figure 4 Eligibility Evaluation in the Open-Label Phase (Example 4)

QRV in Part 2 is Week 36, and if a subject does not meet the criteria, subsequent injections will not be performed, and Week 48 completion visit will be performed.

3. INTRODUCTION

3.1. Study Rationale

GSK1358820, botulinum toxin type A (hereafter referred to as the product) is sterile, purified type A botulinum neurotoxin complex. Intramuscularly injected botulinum neurotoxin shows muscle relaxant effects by blocking the neuromuscular junction and inhibiting the release of acetylcholine, a neurotransmitter. Since the approval of the product for strabismus and blepharospasm in US in 1989, the product is licensed for the treatment of various diseases, which respond to the muscle relaxant effects in more than 90 countries (as of Apr 2017).

In Japan, the product is licensed with 8 indications as an ethical drug so far: blepharospasm as first indication in Oct 1996, followed by “hemifacial spasm” in Jan 2000, “spasmodic torticollis” in Jun 2001, “talipes equinus associated with lower limb spasticity in paediatric patients two years of age and older with cerebral palsy” in Feb 2009, “upper limb spasticity” and “lower limb spasticity” in Oct 2010, “severe primary maschalephidrosis” in Nov 2012, and “strabismus” in Jun 2015. For “upper limb spasticity,” 240 units of the product is approved as a maximum dose per administration.

This study is a multicenter, double blind, placebo controlled phase III domestic study in patients with upper limb spasticity and aims to confirm the efficacy and safety of 240 units of the product for post-stroke upper limb spasticity. The information of 400 units of the product in the study is expected to provide beneficial information because the treatment with 240 units of the product with a maximum dose per administration is considered to be insufficient in some patients with post-stroke upper limb spasticity.

3.2. Background

Spasticity is a movement disorder that is characterized by increased myotatic reflex and is regarded as one of positive signs of the upper motor neuron signs (Kagamihara, 2012; Lance, 1980). Spasticity is caused by central nerve system injuries such as stroke, traumatic brain injury, or spinal cord injury and chronic neuropathies such as cerebral palsy or multiple sclerosis, etc. Abnormal postures of the upper limbs due to spasticity include thumb refraction, a clenched fist deformity, flexion of the wrist flexors, pronation of the forearms, flexion of the elbow flexors, and adduction/inner rotation of the shoulder flexors (Gracies, 2003; Kinoshita, 2015).

Spasticity hampers rehabilitation therapy. In addition, limitation of flexors range of motion and persistent pain hinder from caregiving and decrease activity in daily life (Grazko, 1995); therefore, many of patients with stroke require treatments to ameliorate their dysfunction.

For the treatments of spasticity, rehabilitation therapy, oral medications, phenol blocks, and baclofen injections were used until botulinum therapy has been approved as a national health insurance coverage. These treatments were commonly challenging because of lack of effects, difficult procedures, or invasive interventions. Subsequently, in Oct 2010, the product was approved as a botulinum treatment for upper and lower limb spasticity in Japan. Since then, botulinum toxin has been used for the treatment of spasticity (Ohsawa, 2013). According to the “Japanese Guidelines for the Management of Stroke” (initial version in 2009, revised in 2015) (Ogawa, 2015; Shinohara, 2009), which was issued by the Japan Stroke Society, botulinum therapy is recommended for the treatment of spasticity as Grade A, and is considered to be effective for relief of upper limb spasticity, increase of range of motions in flexors, and reduction of the amount of assistance on daily life.

In Japan, upper limb spasticity, a domestic phase II study involving the finger, wrist, and elbow flexors was performed from Dec 2001 through Mar 2003, and a domestic phase III study involving the finger and wrist flexors from May 2007 through Dec 2008. Consequently, the product was approved for the treatment of upper limb spasticity with a maximum dose of 240 units per administration in Oct 2010.

However, subsequently, the injections of the product at 240 units were found to be insufficient for the involving muscles because patients with extensive upper limb spasticity require dose adequate to inject into many of the involving muscles. Therefore, many medical institutions requested us to increase the maximum dose per administration of the product. Moreover, the specified drug-use survey from Jun 2011 through Apr 2014 identified that approximately 39% of the patients who use the product for upper limb spasticity were injected more than 240 units, a maximum dose per administration. The results suggest high patient needs for an increase of the maximum dose per administration of the product.

In US, as a maximum dose per administration, 400 units of injections of the product have been approved for the treatment of upper limb spasticity in adult patients in 2015; therefore, the authorized dose between US and Japan is different.

Based on these background, the study was planned to evaluate the efficacy and safety of 400 units of the product for upper limb spasticity in order to increase the maximum dose per administration to 400 units.

The study was planned based on the regulatory advice by the Pharmaceuticals and Medical Devices Agency (PMDA).

3.3. Benefit/Risk Assessment

For details of the known and anticipated benefit/risk and rationally expected adverse events are shown on the Investigator's Brochure (IB) and package insert.

3.3.1. Risk Assessment

| Important identified risks | Reports suggesting risks/ Outlines of rationale | Measures for risk minimization |
|--|--|--|
| Investigational product: GSK1358820 | | |
| Hypersensitivity | Serious and/or immediate hypersensitivity reactions (anaphylaxis, serum sickness, urticarial, soft tissue edema, or dyspnea, etc.) have been rarely reported. | Patients who previously experienced allergic reactions due to botulinum toxin type A, an additive agent of sodium chloride, or human serum albumin are excluded from enrolment. Upon written informed consent process, subjects will be explained that any urticarial, swelling face, throat swelling, wheezing, dizziness, or dyspnoea should contact their investigator. |
| Pre-existing neuromuscular disorder | Patients with neuromuscular junction diseases (myasthenia gravis, Lambert-Eaton myasthenic syndrome etc.) may increase the sensitivity to the product, resulting in excessive muscular weakness. | For patients with myasthenia gravis, Eaton-Lambert syndrome (ELS), amyotrophic lateral sclerosis, or a serious disease and who use a concomitant drug (s) which may inhibit neuromuscular function, exclusion criteria will be set, and those patients will be excluded from enrolment in the study (refer to 6.2.1). |
| distant spread of toxin | Adverse drug reactions in the remote muscles, except but the injected site, have been rarely reported. The adverse drug reactions include muscular weakness, constipation, dysuria, swallowing difficult, and non-accidental entering of food or fluid in the lungs not via the stomach, but the trachea (pneumonia may occur). The patients who received the product at a higher dose are considered likely to have increased risks for these adverse drug reactions. | In this study, a high dose of 400 units of the product will be injected. Therefore, the subjects will be followed up after 2, 4, 6, and 12 weeks of injection. The safety of the subjects will be observed carefully. Use of at least one of the following guide tools (electromyogram, electrical stimulator, or ultrasonography) will be essential in the blind phase to ensure identification of the exact site of injection. |

| Important identified risks | Reports suggesting risks/ Outlines of rationale | Measures for risk minimization |
|--|---|--|
| Immunogenicity, drug resistance, antibody production | The important cause of neutralizing antibody production has not been fully clarified. A few studies suggested that the injection of the product at short intervals or at a high dose may lead to increased rate of antibody production[Jankovic, 2006; Klein, 2002]. Neutralizing antibody production against botulinum toxin type A may lead to inactivation of the biological activity of the product, resulting in decreased therapeutic effects of the product. | In this study, patients who were considered likely to have neutralizing antibody production based on the previous treatment experience of botulinum toxin type A will be excluded from enrolment in the study (Exclusion Criteria 6.2.1). In addition, treatment schedule in the study was set to ensure at least a 12-week dosing interval. |
| Other (If applicable) | | |
| Medication error (preparation with lidocaine) | One fatal case due to anaphylaxis has been reported. In this case, the patient died after 100 units of an injection of the product that prepared inappropriately with 5 mL of 1% lidocaine. The causal relationship of death to the product and lidocaine, or both has been unknown. | In this study, the product will be prepared appropriately with 0.9% normal saline. The preparation method will be described on the study reference manual (SRM). |

3.3.2. Benefit Assessment

In patients with post-stroke upper limb spasticity, currently, the product is approved to inject up to 240 units per administration in Japan. However, in patients with extensive upper limb spasticity, the treatment effects of the product are presumed to lack because of the dose limitation.

In US, the efficacy and safety of the product up to 400 units per dose for patients with upper limb spasticity is confirmed, and the clinical use of the product has been approved. The injections of 400 units of the product in this study are expected to increase injectable sites and enhance the treatment effects in Japanese patients with upper limb spasticity, who did not have great benefits from 240 units of the product.

If a subject is assigned to the 240 units group in Part 1 and meets the eligibility criteria for injection in the open-label phase, 400 units of the product will be injected in and after Part 2. Therefore, all the subjects who participate in this study are given the opportunity to receive 400 units of the product (Refer to “[5. STUDY DESIGN](#)”).

3.3.3. Overall Benefit:Risk Conclusion

The known potential risks in the product is justified by the benefits which would provide for the patients with post-stroke upper limb spasticity, given the safety measures to minimize risks in subjects who enrol in the study.

4. OBJECTIVES AND ENDPOINTS

| Objectives | Endpoint(s) |
|--|---|
| Primary | |
| To evaluate the efficacy of injection of 400 units of the product at Week 6 (finger/ wrist flexors: 240 units, elbow flexors: 160 units), comparing to that of 240 units (finger/ wrist flexors: 240 units, elbow flexors: placebo). | The rate of the subjects that Modified Ashworth Scale (MAS) score was reduced at least 1 from baseline in the elbow flexors (the responder rate). |
| Secondary | |
| To evaluate the efficacy of 400 units of the product, comparing to 240 units of the product. | <ul style="list-style-type: none"> • The responder rate of MAS score from baseline in finger, thumb and wrist flexors • Changes in MAS score from baseline in finger, thumb, wrist, elbow, pronation of forearms and shoulder flexors • Changes in Disability Assessment Scale (DAS) from baseline |
| To evaluate the safety and tolerability of the product of 400 units, comparing to 240 units of the product/ To evaluate the safety and tolerability of 400 units of the product. | <ul style="list-style-type: none"> • Adverse events • Physical examinations • Clinical laboratory tests (haematology, blood biochemistry, urinalysis) • Vital signs (heart rate, blood pressure, body temperature) |
| Exploratory | |
| To evaluate the efficacy of 400 units of the product | <ul style="list-style-type: none"> • Changes in MAS score from baseline in finger, thumb, wrist, elbow, pronation of the forearm and shoulder flexors |
| To evaluate the other efficacy of the product of 400 units, comparing to 240 units of the product/ To evaluate the other efficacy of 400 units of the product | <ul style="list-style-type: none"> • Changes in Numeric Rating Scale (NRS) for pain from baseline • Changes in other items of DAS from baseline • Clinical Global Impression of Change (CGI) of functional disability by an investigator • CGI of functional disability by a patient • Time to patient-reported onset of spasticity symptom relief • Patient-reported benefit of injection • Time to qualification for retreatment |
| To evaluate neutralizing antibody production | <ul style="list-style-type: none"> • Testing for neutralizing antibody |

5. STUDY DESIGN

5.1. Overall Design

This study is a 48-week multicenter, phase III study (a placebo controlled, randomized, double-blind comparative study and an open-label, uncontrolled study) to evaluate the efficacy and safety of the product in patients with post-stroke upper limb spasticity. The study period is up to 52 weeks, consisting of a screening phase up to 4 weeks, minimum 12-week blind phase (Part 1), maximum 36-week open-label phase (12 weeks per cycle with maximum 3 treatment periods, Part 2, Part 3 and Part 4). (Figure 5).

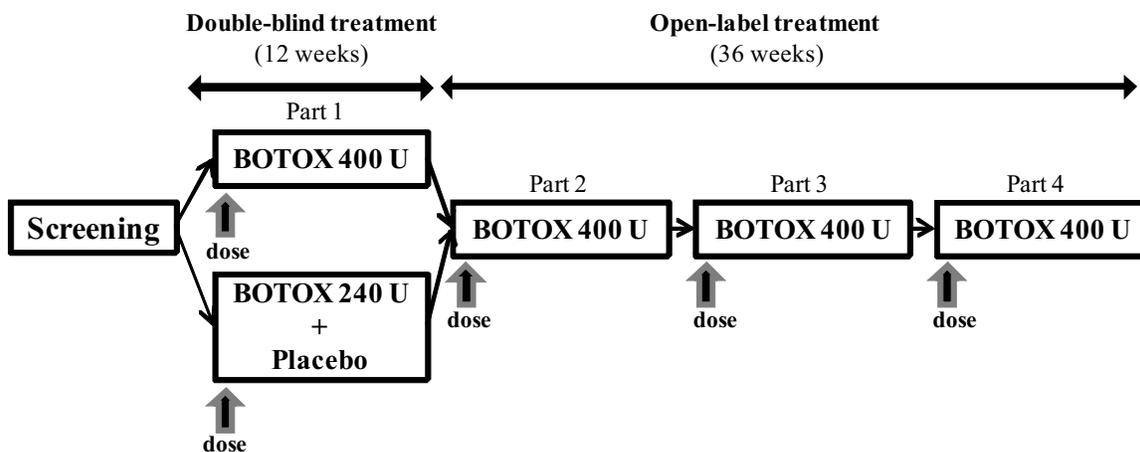


Figure 5 Study Design

In this study, the efficacy of 400 units of the product at Week 6 is evaluated, comparing to that of 240 units, and improvement tendencies are also evaluated in patients with post-stroke upper limb spasticity. The improvement will be defined as at least 1 reduction on the MAS score from baseline (a measurement value before injection of Day 1). The responder rate (the rate of the subjects that MAS score is reduced at least 1 from baseline) in the elbow flexors at Week 6 is set as an endpoint. As a point estimate, if the responder rate in the 400 units group outweighs that in the 240 units group, improvements tendencies will be considered to be positive.

For injection, use of the following any one of the tools: EMG, electrical stimulator, or ultrasonography, is recommended to ensure identification of the exact injection site. In the blind phase, use of at least one of the following tools: EMG, electrical stimulator, or ultrasonography, will be essential to ensure identification of the muscle to be injected correctly.

5.1.1. Screening Phase (up to 4 weeks)

Evaluation and screening tests will be performed 28 days to 7 days (+3 days) before initial injection (Day 1) as a starting point. The investigator will decide which arm to be injected during screening phase. Throughout the study period, the arm, which is decided to be injected at screening phase will be involved during the injections and evaluations, unless clearly specified otherwise by the sponsor.

5.1.2. **Blind Period (minimum 12 Weeks): Placebo Controlled, Randomized, Double Blind Design**

Subjects who meet the inclusion criteria will be randomized 1:1 to either the 400 units or the 240 units group.

- In the 400 units group, a total of 240 units of the product will be injected into the muscles that act on the finger (including thumb flexors) and wrist flexors, and a total of 160 units into the muscles that act on the elbow flexors; a total of 400 units of the product will be injected.
- In the 240 units group, a total of 240 units of the product will be injected into the muscles that act on the finger (including thumb flexors) and wrist flexors. Placebo will be injected into the muscles that act on the elbow flexors. A total of 240 units of the product will be injected.

If the total dose for the muscles that act on the finger and wrists flexors is ensured by 240 units, and 160 units for the muscles that act on the elbow flexors, the dose can be adjusted at an investigator's discretion based on the subject's symptoms. (Refer to "7.1. Treatments Administered" Table 2).

5.1.3. **Open-Label Phase (maximum 36 weeks): Uncontrolled, Open-Label Design**

The product of 400 units will be injected in both groups. The product can be injected up to 3 times after completion of Part 1 in the blind phase. In the open-label phase, subjects whom the investigator considers eligible for the injection will be treated (Refer to 5.1.3.1. Eligibility Criteria for Injection in and after Part 2). The next injection cannot be performed until the eligibility of the subject has been confirmed by the investigator (Refer to 5.1.3.1. Eligibility Criteria for Injection in and after Part 2).

In the open-label phase, the muscle to be injected and the dose will be decided by the investigator based on the patient's symptoms, and a total dose of 400 units of the product will be injected in a divided dose (Refer to "7.1. Treatments Administered" on Table 3). For the muscles that the investigator considers unnecessary to be treated, an injection may be skipped. The involving muscle and the dose do not have to be same each time always.

5.1.3.1. **Eligibility Criteria for Injection in and after Part 2**

In the open-label phase (Part 2, Part 3, and Part 4), the subjects whom the investigator considers eligible for the injections in the open-label phase only will be treated. The eligibility is evaluated at a study visit after Week 12 (V5, if a subject does not meet the eligibility criteria, the evaluation will be performed at QRV (Qualification for Retreatment Visit). A subject will be considered as eligible when he or she meets all the criteria. The eligibility evaluation will be performed after completion of Part 1 in the blind phase, between Week 12 to Week 36. If a subject does not meet the eligibility at Week 36, subsequent evaluation will not be performed, and the product cannot be given (refer to Figure 1, Figure 2, Figure 3, and Figure 4).

- 1) At least 12 weeks (84 days) have passed since the preceding dose
- 2) Among the finger, wrist or elbow flexors, 2 flexors have at least 2 on the MAS (except only the finger and wrist flexors of 2 on the MAS)
- 3) Subject who request the injection

- 4) Subjects whom an investigator considers an injection of 400 units of the product is appropriate
- 5) Subjects who have not experienced serious adverse events (SAE) associated with the injection of the product

If subjects meet the criteria of the above 1) to 5) at V5 or QRV, body weight measurement, ECG, pulmonary function test, and pregnancy test will be performed to evaluate the following items. If subjects meet the following 6) to 8), the subjects will move forward to V1.

A pulmonary function test must be performed at V5 even if subjects do not meet the above 1) to 5) in accordance with the study operation schedule (SoA).

- 6) Body weight ≥ 40 kg
- 7) Subjects who the investigator considers there are no unacceptable safety concerns [potential for serious adverse events, electrocardiogram (ECG) or abnormal pulmonary function value*] due to 400 U of BOTOX
* This study will use SpO₂ (oxygen saturation) as a parameter of pulmonary function. A subject who has a $\geq 3\%$ reduction from the pre-injection SpO₂ (Day 1) in post-injection SpO₂ or whose SpO₂ value is $< 95\%$ should be referred to a pulmonologist. A subject with pulmonary dysfunction due to study treatment also should be referred to a pulmonologist. If the subject is considered by the pulmonologist to have no concerns about pulmonary function, the investigator should carefully consider whether to start the study treatment.
- 8) Women of childbearing potential who have negative pregnancy test result in urine

5.2. Number of Participants

Approximately 120 subjects (approximately 60 in each group) will be randomized to obtain an evaluable subject sample of approximately 100 at Week 48 as subjects who complete the study

5.3. Participant and Study Completion

Subjects who completed all the study procedures, including a completion visit will be regarded as study completion. The completion date in this study will be defined as the last day performing the study procedure of last subject.

5.4. Scientific Rationale for Study

The study design was set to evaluate the efficacy and safety of 400 units of the product in patients with post-stroke upper limb spasticity. The primary endpoints employed the responder rate of the MAS score in the elbow flexors. The reasons for employing MAS score as an indicator include that MAS is highly reliable for evaluation of upper limb spasticity (Bohannon, 1987; Mutlu, 2008); especially, for evaluation of spasticity in the elbow flexors in the upper limbs (Gregson, 2000; Sloan, 1992).

Screening Phase

The screening phase up to 28 days before initial injection was set in order to confirm subjects meet the inclusion criteria and none of the exclusion criteria, and assess the condition of subjects at baseline.

However, measurements of laboratory parameters at screening phase should be completed by 4 days before Day 1 (Day -28 to -4).

Treatment Phase

In Part 1, a double blind comparative study was set to compare the efficacy of the product of 400 units to 240 units, the currently approved dose for upper limb spasticity. In the blind phase, 240 units of the product will be injected into the muscles that act on the finger (including the thumb)/wrist flexors, and 160 units (the 400 units group) or placebo (the 240 units group) for the muscles that act on the elbow flexors. The improvement tendencies in the efficacy between the 240 units group, the total dose, and the 400 units groups will be compared by evaluating the responder rate tendencies on the MAS score in the elbow flexors in a blinded manner. In the previous confirmatory study (108509 study) for approval of the product for upper limb spasticity, the elbow flexors were not involved. Therefore, in this study, the responder rate on the MAS score in the elbow flexors was decided to compare as the placebo group.

Actually, in medical institutions, the product is injected into the whole upper limb, including the shoulder flexors. In addition, the dose for each muscle is decided at an investigator's discretion. Previous studies reported that botulinum injections into the pectoralis major and teres major muscle relieved pain in patients with hemiplegia (Marciniak, 2012) and injections into the sub-scapula improved passive range of motion (Yelnik, 2007). Therefore, in and after Part 2 in the open-label phase, the product will be allowed to be injected not only into the muscles that acts to the finger (including the thumb), wrist, and elbow flexors, but also the muscles that act on the shoulder flexors, where applicable, enabling an investigator to decide the dose for each muscle. In addition, the study design included safety evaluation of the product at Week 48 after initial injection in all subjects as far as possible for safety evaluation purposes of 400 units.

5.5. Dose Justification

The product of 400 units is a maximum dose for upper limb spasticity, which was approved by the U.S. Food and Drug Administration (FDA), and this suggests that the efficacy and safety profiles are favourable. Evaluation of the efficacy and safety of 400 units of the product provides beneficial information in Japanese patients with severe post-stroke upper limb spasticity, who are considered injections of 400 units of the product are necessary.

The dose of 240 units of the product, the controlled group, in the blind phase (Part 1) is the current authorized dose (a maximum dose per administration) for upper limb spasticity in Japan. In this study, the 240 units group was set as the control group in order to evaluate improvement tendencies, comparing the efficacy of 240 units of the product, the current approved dose, to that of 400 units of the product.

6. STUDY POPULATION

Inclusion of subjects despite expectation of deviation from the protocol, namely, exemption or discharge from the protocol, cannot be allowed.

6.1. Inclusion Criteria

6.1.1. Screening Phase (Day -28 to Day -1)

In the screening phase, subjects eligible for enrolment in the study must meet all of the following criteria. Laboratory parameters should be measured by 7 days (\pm 3 days) before initial injection (Day 1).

Age

1. Between 20 and 80 years of age at the time of informed consent (ICF).

Subjects and Characteristics of the Disease

2. Patients with at least a 3-month history of upper limb spasticity after the most recent stroke
3. Patients who have spastic symptoms in the finger (including the thumb), wrist, and elbow flexors whom the investigator considers the injections of 400 units of the product is necessary for the upper limb based on the muscle spasms and the symptoms of the patient
4. Patients who have a previous treatment history of 240 units of the product for the upper limb at least 16 weeks before screening (refer to [Table 3](#) for muscles in the upper limbs)
5. Patients who meet following criteria on MAS at screening (Test position: sitting)
 - At least 3 in for the elbow flexors
And
 - At least 2 in the finger or wrist flexors
6. Patients who have severe upper limb spasticity, which deserves to be treated with 400 units of the product in the divided dose and was previously injected 240 units of the product
7. Patients whom the investigator considers that enrolment in the study poses no problems based on the laboratory data results at screening
8. Patients who are free from a history of acute decreased lung function (hospitalization with aggravated asthma/COPD, pneumonia, or signs of pneumonia, or abnormal reactive airway diseases suggested on X-rays) within the last 3 months at screening and have stable pulmonary function (SpO₂ value is \geq 95%)

Body Weight

9. Body weight \geq 40 kg at screening

Sex

10. Male or female

a. Male Subjects

Male subjects must content to use highly effective contraceptive methods, which are shown on attachment 5 of the protocol in detail during the study period, and sperm donation must be avoided.

b. Female Subjects

Female subjects who are not pregnant or lactating are considered eligible (refer to attachment 5) if at least one of the following criteria is met:

- i) Non-childbearing potential based on the definition on attachment 5

- ii) Women of childbearing potential who content to follow the guidance about contraception on attachment 5 during the study period and at least for 3 months after the last dose of the product.
- iii) No plan of pregnancy during the study period

Informed Consent

11. Patients who have ability to sign their name on the ICF, following the description on attachment 3, adhering to the requirements and limitations described on the ICF and the protocol.

6.1.2. Day 1 (prior to injection)

Subjects eligible for enrolment in the study must meet all of the following criteria on Day 1 (prior to injection):

Subjects and Characteristics of the Disease

31. Patients who meet the following criteria on MAS score: (Test position : sitting)
- At least 3 in the elbow flexors
- And
- At least 2 in the finger or wrist flexors

Preceding Treatments and Concomitant Medications/Therapies

32. If centrally acting muscle relaxants, tetracycline antibiotics, anticholinergics, benzodiazepines, or benzamides are given, the dose and regimen must be stable at least for the last 2 months before Day 1; Patients who can maintain the same dosage and regimens at least in the blind phase after initial injection (dose reductions and discontinuation of the drugs are acceptable in the open-label phase. However, second dose increase, resumption, and or new treatment will not be performed).
33. If intrathecal baclofen is given, the dose and regimen must be stable at least for the last 1 month before Day 1; Patients who can maintain the same dosage and regimens at least in the blind phase after initial injection (intravenous bolus is not acceptable, dose reductions and discontinuation of the drugs are acceptable. However, second dose increase, resumption, and or new treatment will not be performed).
34. If antiepileptic agents are given, the dose and regimen must be stable at least for the 1 month before Day 1; Patients who can maintain the same dose and regimens at least in the blind phase after initial injection (dose reductions and discontinuation of the drugs are acceptable in the open-label phase. However, second dose increase, resumption, and new treatment will not be performed).
35. If a physical therapy, occupational therapy, or a static splint on the study involvement upper limbs is given, the frequency and treatment regimen must be stable at least for the last 3 weeks before Day 1; Patients who can maintain the same dose and regimens at least in blind phase (In the open-label phase, the frequency and treatment regimen can be changed depending on the condition of spasticity).

6.2. Exclusion Criteria

6.2.1. Screening Phase (Day -28 to Day -1)

A subject will be excluded from enrolment in this study if any of the following criteria apply in the screening phase. Measurements of laboratory parameters at screening must be completed 7 days (± 3 days) before initial injection (Day 1).

Medical Condition

1. Patients present with spasticity requiring treatment in the non-paralytic side of the upper limb
2. Patients who have fixed contracture* in the finger (upper limb), wrist, elbow or shoulder muscle, which will be involved in the study
(*Positive effects were not confirmed in the previous treatment with GSK1358820, and contracture is considered to be the main cause of limited range of motion in the joint.)
3. Patients who have medically significant capsulitis or subluxation in any one of the fingers (upper limb), wrist, elbow and shoulder, which will be involved in the study, or whom an investigator considers the complicated local signs of pain may affect the efficacy evaluation
4. Patient's upper limb spasticity is attributed to other than stroke (traumatic brain injury, spinal cord injury, multiple sclerosis, or cerebral palsy)
5. Patients who have a 2-fold higher alanine aminotransferase (ALT) level than the upper limit of normal (ULN)
6. Patients who have a 1.5-fold higher bilirubin than the ULN (If a bilirubin fractionation shows direct bilirubin $< 35\%$, a 1.5-fold higher free bilirubin than the ULN is acceptable).
7. Patients whom the investigator considers presence of a current medical history of unstable liver diseases or biliary tract diseases (the condition will be defined by development of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice or hepatic cirrhosis)
Note:
 - If a patient with stable chronic liver diseases (Gilbert's syndrome, silent gallstone, and stable chronic hepatitis B or hepatitis C [Namely, hepatitis B surface antigen: HBsAg or hepatitis C virus: HCV antibody shows positive at screening or within 3 months before initiation of the study treatment] are included) meets other inclusion criteria, the patient can be enrolled in the study.
8. Patients with QTc > 450 msec or QTc > 480 msec in patients with bundle branch block
Note:
 - QT intervals corrected by the Bazett method (QTcB); QT intervals corrected by the Fridericia method (QTcF) and/or QT intervals corrected by other methods; interpretation by a machine or manual re-interpretation will be used.
 - Prior to study initiation, the correction formula which is used for the subject's inclusion/exclusion/discontinuation criteria will be determined. Namely, several different correction formulae cannot be used for calculation of QTc in each subject. In addition, the lowest QTc level cannot be used for enrolment or discontinuation of subjects of the study.

Preceding Treatments and Concomitant Medications/Therapies

9. Patients who use peripherally acting muscle relaxants (dantrolene sodium, suxamethonium chloride, pancuronium bromide, vecuronium bromide, rocuronium bromide, etc.) within 1 week of screening.
10. Patients who use antibiotic agents with neuromuscular junction inhibitory effects: Aminoglycoside antibiotic agents (streptomycin sulfate, kanamycin sulfate, gentamicin sulfate, neomycin sulfate, spectinomycin hydrochloride, etc.), polypeptides (polymyxin B sulfate), lincomycins (lincomycin hydrochloride, clindamycin), and enviomycin sulfate within 1 week of screening.
11. Patients who was diagnosed as having a malignant tumor, or have a history of a malignant tumor within the last 5 years (except completely resected basal cell carcinoma or planocellular carcinoma at least 12 weeks before screening)

Previous Experience of Participation in a Clinical Studies/Current Participation in another Ongoing Study

12. Patients who have participated in another study of an investigational product or other medical research (a clinical study of pharmacotherapy, non-pharmacotherapy, or interventional device) within 30 days before screening, or are currently participating in a study

Evaluation by Diagnosis

13. Patients who are concerned likely to have an increased risk for an underlying medical condition/neurological disease due to exposure of the product; patients who have myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or a serious disease and use of a concomitant drug which may inhibit neuromuscular function
14. Patients with antihuman immunodeficiency virus (HIV) antibody positive
15. Patients who previously experienced allergic reactions or hypersensitivity due to botulinum toxin type A, an additive agent of sodium chloride, or human serum albumin
16. Patients who were previously suspected to have neutralizing antibody production by an investigator during an injection of botulinum toxin type A
17. Patients who have a skin disease such as infection at the site to be injected
18. Patients who suffer from serious and unstable disease, which could pose problems for the safety of subjects and study procedure compliance

6.2.2. Day 1 (Prior to injection)

A subject will be excluded from enrolment in this study if any of the following criteria apply on Day 1 (prior to injection):

Medical condition

31. Patients who have aspiration pneumonia, relapse of lower respiratory tract infection, uncontrollable asthma, uncontrollable COPD, and/or underlying or a history of serious respiratory dysfunction, which were clinically considered to be respiratory function impairment (e.g., SpO₂ <95%) by an investigator within 12 months before Day 1 visit
32. Patients who have a history of aspiration, or an underlying and/or a history of the symptoms that suggests high risks for aspiration by an investigator within 12 months before Day 1 (serious salivation requiring changing in a type of diet, chronic dysphagia that is difficult to swallow)

Preceding Treatments and Concomitant Medications/Therapies

33. Patients who were treated with botulinum toxin for spasticity of upper limb less than 16 weeks before Day 1 visit
34. Patients who underwent surgical interventions, phenol block, ethanol block or Muscle Afferent Block (MAB) within 12 months before Day 1 visit, or these interventions are planned during the study period in any one of the finger (upper limb), wrist, elbow or shoulder muscles, which will be involved in the study
35. Patients who placed a surgical cast or a dynamic splint within 3 months before Day 1 study visit, and/or these interventions are planned to be placed on the upper limb to be involved in the study
36. Patients who were injected corticosteroid or an anesthetic agent into the finger (upper limb), wrist, or shoulder flexors, which will be involved in the study within 3 months before Day 1 visit, or these injections are planned during the study
37. Patients who received CIMT (constraint-induced movement therapy) within 3 months before Day 1 visit or CIMT is planned during the blind phase
38. Patients who underwent ultrasound therapy, TENS (transcutaneous electrical nerve stimulation), electrical stimulation therapy, or acupuncture therapy in the upper arm, which will be involved in the study within 1 month before Day 1 visit, or these therapies are planned during the study

6.3. Lifestyle Restrictions

No limitations are required.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently [randomized/entered in the study]. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Rescreening

If a patient does not meet the participation criteria in the study (dropout during screening), the patient may undergo second screening only 1 time. If a patient does not meet following items, contact the medical monitor of the sponsor and gain his/her consent because validity of rescreening in subjects who dropped out needs to be judged carefully in the light of medical aspects.

- Subjects who did not meet the inclusion criteria for MAS (Inclusion criteria 5 at screening) and dropped out (However, the dropout period will be for within only 1 month from the dropout).
- For some reasons, a subject cannot make a study visit or undergo examination
- Sample collection or examination cannot be performed because of procedural or technical problems

The investigator must carefully consider the ethical aspects of subjects, and if other treatments are considered to give more treatment benefits for a subject, rescreening must not be conducted.

The rescreened subjects will be allocated a different subject identification number as upon initial screening.

7. TREATMENTS

Study treatment product is defined as any investigational treatment(s), and placebo to administer to a study participant according to the protocol.

7.1. Treatments Administered

| | | | |
|---|--|-----------|---|
| Study Treatment Name: | GSK1358820 (Nonproprietary name: Botulinum toxin type A) | | Placebo |
| Dosage formulation: | Injection | | Injection |
| Ingredient and quantity (Per vial) | Botulinum toxin A 100 units Sodium chloride 0.9 mg Human serum albumin 0.5 mg | | Sodium chloride 0.9 mg |
| Packaging and Labeling | It will be listed on the labelling in accordance with the regulatory requirements in Japan. | | It will be listed on the labelling in accordance with the regulatory requirements in Japan. |
| Manufacturer | Allergan (Ireland) | | Allergan (Ireland) |
| Dose | 400 units | 240 units | Dose |
| Dosing instructions | <p>Part 1: 240 or 400 units of the product will be injected into the muscles that act on the finger (including thumb flexors), wrist and elbow flexors, in accordance with Table 2. In and after Part 2: 400 units of the product will be injected into the muscles that act on the finger (including thumb flexors), wrist, elbow and shoulder flexors in accordance with Table 3. For the muscles that the investigator considers unnecessary to be treated, an injection may be skipped. Dose intervals should be at least 12 weeks.</p> <p>For adjustment of the product, the product will be dissolved with 2 ml of normal saline per 1 vial (100 units). The details will be described on Table 4.</p> | | |

In the blind phase

- A total of 240 units of product will be injected into the muscles that act on finger (including thumb flexors) and wrist flexors, and a total of 160 units of the product or placebo for the muscles that act on the elbow flexors in divided doses in accordance with [Table 2](#).
- The muscles which are not listed on [Table 2](#) must not be used.
- All of the muscles described on [Table 2](#) must be used. If the subject with no symptoms with thumb, the investigator does not have to inject to thumb.
- If the total dose for the muscles that act on the finger and wrists flexors is ensured by 240 units, and 160 units for the muscles that act on the elbow flexors, the dose can be adjusted at an investigator's discretion based on the symptoms of a subject.

In the open-label phase

- The investigator will decide the dose and the muscle to be injected based on the symptoms of patients, and a total of 400 units will be injected in divided doses. For the muscles that the investigator considers unnecessary to be treated, an injection may be skipped.
- The muscles to be injected must be chosen from [Table 3](#), and the muscles which are not listed on [Table 3](#) must not be used. For dose and number of injection site (sites/muscles), refer to [Table 3](#) and will be decided by investigator.

Table 2 Muscle Involvement and Dose in the Blind Phase

| Number | Muscles | The 400 units group Dose (units) | The 240 units group Dose (units) | Number of injection site (site and muscles) ³ | Joint |
|--------|--------------------------------|-------------------------------------|-------------------------------------|--|----------|
| A1 | Biceps brachii | 70 ¹ | Placebo | 2 | A.Elbow |
| A2 | Brachialis | 45 ¹ | | 1 | |
| A3 | Brachioradialis | 45 ¹ | | 1 | |
| B1 | Flexor carpi radialis | 50 ² | 50 ² | 1 | B.Wrist |
| B2 | Flexor carpi ulnaris | 50 ² | 50 ² | 1 | |
| C1 | Flexor digitorum profundus | 50 ² | 50 ² | 1 | C.Finger |
| C2 | Flexor digitorum superficialis | 50 ² | 50 ² | 1 | |
| D1 | Flexor pollicis longus | 20 ² | 20 ² | 1 | D.Thumb |
| D2 | Adductor pollicis | 20 ² | 20 ² | 1 | |
| | Total | 400 ² | 240 ² | 1 | - |

1: Within the limits of the total of 160 units (the elbow flexors), the dose will be decided by an investigator depending on the patient's symptoms.

2: Within the limits of the total of 240 units (the finger and wrist flexors), the dose will be decided by an investigator depending on the patient's symptoms.

3: When the dose exceeds 50 U per muscle, take into account the divided-injection.

Table 3 Muscle Involvement and Reference Dose in the Open-Label Phase
(Modified partially of "Dosing, Administration, and a Treatment Algorithm for Use of Botulinum Toxin A for Adult-Onset Spasticity. [Brin, 1997]")

| Number | Muscles ¹ | Dose (units) ² | Number of injection site (Sites/muscles) ² | Joint |
|--------|--------------------------------|---------------------------|---|------------|
| A1 | Biceps brachii | 50-200 | 4 | A.Elbow |
| A2 | Brachialis | 25-75 | 2 | |
| A3 | Brachioradialis | 25-75 | 2 | |
| B1 | Flexor carpi radialis | 25-100 | 2 | B.Wrist |
| B2 | Flexor carpi ulnaris | 10-50 | 2 | |
| C1 | Flexor digitorum profundus | 25-100 | 2 | C.Finger |
| C2 | Flexor digitorum superficialis | 25-75 | 4 | |
| C3 | Lumbricales interossei | 10-50/hand | 3 | |
| D1 | Flexor pollicis longus | 5-25 | 1 | D.Thumb |
| D2 | Adductor pollicis | 5-25 | 1 | |
| D3 | Opponens | 5-25 | 1 | |
| E1 | Pronator teres | 25-75 | 1 | E.Forearms |
| E2 | Pronator quadratus | 10-50 | 1 | |
| F1 | Teres major | 25-75 | 1 | F.Shoulder |
| F2 | Latissimus dorsi | 50-150 | 4 | |
| F3 | Pectoralis major | 75-150 | 4 | |
| F4 | Subscapularis | 25-75 | 1 | |

(Brin MF and the Spasticity Study Group, 1997)

1: The muscles which are not listed on Table 3 must not be used

2: For dose and number of injection site (sites/muscles), refer to Table 3 and will be decided by investigator.

Table 4 Muscle Involvement and Reference Dose in the Open-Label Phase

| Dose (units) | Injection Volume (ml) |
|--------------|-----------------------|
| 100 | 2.0 |
| 95 | 1.9 |
| 90 | 1.8 |
| 85 | 1.7 |
| 80 | 1.6 |
| 75 | 1.5 |
| 70 | 1.4 |
| 65 | 1.3 |
| 60 | 1.2 |
| 55 | 1.1 |
| 50 | 1.0 |
| 45 | 0.9 |
| 40 | 0.8 |
| 35 | 0.7 |
| 30 | 0.6 |
| 25 | 0.5 |
| 20 | 0.4 |
| 15 | 0.3 |
| 10 | 0.2 |
| 5 | 0.1 |

7.2. Dose Modification

Not applicable

7.3. Method of Treatment Assignment

After completion of all evaluations at screening phase/initiation of the blind phase, the subjects who met the inclusion criteria and none of the exclusion criteria will be given their randomization number at a case registry center and randomized to either the 240 or 400 units group. The assigned randomization number cannot be re-used. The table of the allocation will be prepared via a computer in GSK, using the RandAll systems.

Based on the MAS score (3 or 4) in the elbow flexors, subjects will be stratified at the time of randomization.

The subjects who meet the eligibility for the injections in the open-label phase can move forward to the open-label phase and be injected (Refer to section 5.1.3). In the open-label phase, 400 units of the product will be given to all subjects. Other detailed information will be described on SRM.

7.4. Blinding

This study consists of the blind phase (Part 1), followed by the open-label phase (Part 2 and subsequent Parts), and in the blind phase, following processes are applied.

A Role of the Person Responsible for Investigational Product Assignment

The person who is responsible for investigational product assignment will prepare an operating procedure for the assignment. The operation will be conducted in accordance with the operating procedure. The person who is responsible for the investigational product assignment will display the drug number on a container of the investigational product (investigational product and control drug)

after checking of the investigational product (investigational product and control drug) and the indistinguishability of packaging appearance. The confirmation of the investigational product (investigational product and control drug) and the indistinguishability of packaging appearance will be also performed after completion of the study. In addition, an operating procedure for occasion where the emergency treatment disclosure is required will be prepared. In response to the request of disclosure, unblinding procedures are performed for the requested drug only.

The unblinded subjects by the investigator will discontinue participation in the study. In addition, the major reasons for discontinuation (the event(s) or condition led to unblinding) will be described on case report form (CRF).

The Global Clinical Safety and Pharmacovigilance (GCSP) of the sponsor may disclose the assigned treatment in the subject, who experienced serious adverse events. For serious adverse events requiring emergency report to the regulatory authority, a copy of an emergency report on the assigned treatment of the subject may be sent to the study involving investigator in accordance with the regulations, policy of the sponsor, or both.

7.5. Preparation/Handling/Storage/Control

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual

7.6. Treatment Compliance

Subjects will be intramuscularly injected the product at a medical institution. The injection will be recorded in the source documents, and described in the case report form.

7.7. Concomitant Therapies

The medications that are used by subjects at the time of enrolment in the study or all medications and vaccines to be used during the study (over the counter drugs or prescribed drugs, vitamins, and/or herbal supplements) must be recoded with the following items:

- Reasons for use
- Initial date of administration and administration dates, including completion day
- Regarding the dose, including dosage and number of administration

Contact the medical monitor if there are any questions about concomitant therapies or preceding drugs.

7.7.1. Permitted Concomitant Drugs/Therapies

Following drugs and therapies are permissible only if a subject is already using them before initiation of the study. However, the dosage and administration will not be changed from the screening through completion of the blind phase. In and after open-label phase, dose reduction and discontinuation of the drugs will be allowed. However, once dose is decreased, re-increase will not be performed. If the drug(s) is/are discontinued, the drugs cannot be resumed. No new treatment will not be started after screening phase.

- Central muscle relaxants
(baclofen, tizanidine hydrochloride, eperisone hydrochloride, chlorphenesin carbamate, afloqualone, etc.)
- Tetracycline antibiotics
(tetracycline hydrochloride, doxycycline hydrochloride, minocycline hydrochloride, etc.)
- Anticholinergics
(butylscopolammonium bromide, trihexyphenidyl hydrochloride, etc.)
- Benzodiazepines
(diazepam, etizolam, etc.)
- Benzamides
(tiapride hydrochloride, sulpiride, etc.)
- Antiepileptic drugs
(phenytoin, etc.)
- Intrathecal baclofen therapy

Rehabilitation therapies such as physical therapy, occupational therapy, and static splint are permissible. However, in the blind phase, the frequency and regimens (description of the therapy and intensiveness) for the upper limb, which involves in the study will not be changed. In addition, in the open-label phase, changing rehabilitation therapy to another one that seems to be the most appropriate for a subject is permissible based on the degree of improvements in spasticity. In such cases, the information will be described on CRF. Rehabilitation therapy will not be given on the day of investigational product injection.

Appropriate rehabilitation therapies should be selected from among the following: task-specific training, muscle strengthening exercise, stretching/range of motion (ROM) exercise, splints and orthoses, taping, positioning aid, and others (specify). As for the frequency, the number of days per month, when rehabilitation therapies were performed, between V1 and V5 will be calculated, and the most appropriate frequency will be selected from among the following: not performed, ≤ 8 days per month, > 8 and ≤ 16 days per month, > 16 and ≤ 24 days per month, and > 24 days per month. Details will be provided in the study reference manual (SRM).

7.7.2. Contraindicated Medications/Therapies

Following drugs and therapies will be prohibited to use from screening phase through completion of the study:

- Botulinum toxin preparations
- Peripherally acting muscle relaxants
- (dantrolene sodium, suxamethonium chloride, pancuronium bromide, vecuronium bromide, rocuronium bromide)
- Antibiotic agents with neuromuscular junction blocking effects
 - Aminoglycosides (streptomycin sulfate, kanamycin sulfate, gentamicin sulfate, neomycin sulfate, spectinomycin hydrochloride, etc.)
 - Polypeptides (polymyxin B sulfate)
 - Lincomycins (lincomycin hydrochloride, clindamycin)
 - Enviomycin sulfate
- Nerve blocks such as phenol block, ethanol block and MAB for the upper limb
- Surgical cast or a dynamic splint
- A surgery for the upper limb
- A surgical cast or a dynamic splint for the upper limb
- Corticosteroid injection or an anesthetic agent for the upper limb
- Ultrasound therapy, TENS (transcutaneous electrical nerve stimulation), electrical stimulation therapy, or acupuncture therapy for the upper limb

Following drugs and therapies will be prohibited to use from screening phase through completion of the blinded-phase:

- CIMT (constraint-induced movement therapy)

7.8. Treatments after Completion of the Study

The investigator will take responsibility for subject's medical care after completion of the study, whether the sponsor provides a certain treatment or not.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

The efficacy of the investigational product used in this study sustains for about 3 to 4 months following a single dose, and thus daily dosage is not required; accordingly, treatment discontinuation shall not be defined in this study, and will be considered to be identical to subject withdrawal from this study.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- A subject discontinuing this study must visit the study site for study termination assessment promptly upon decision to discontinue the study.
- Refer to the schedule of assessment (SoA), completion visit (FV), for the details of data to be collected at the study discontinuation, and additional assessment that must be completed.

8.2.1. Liver Chemistry Stopping Criteria

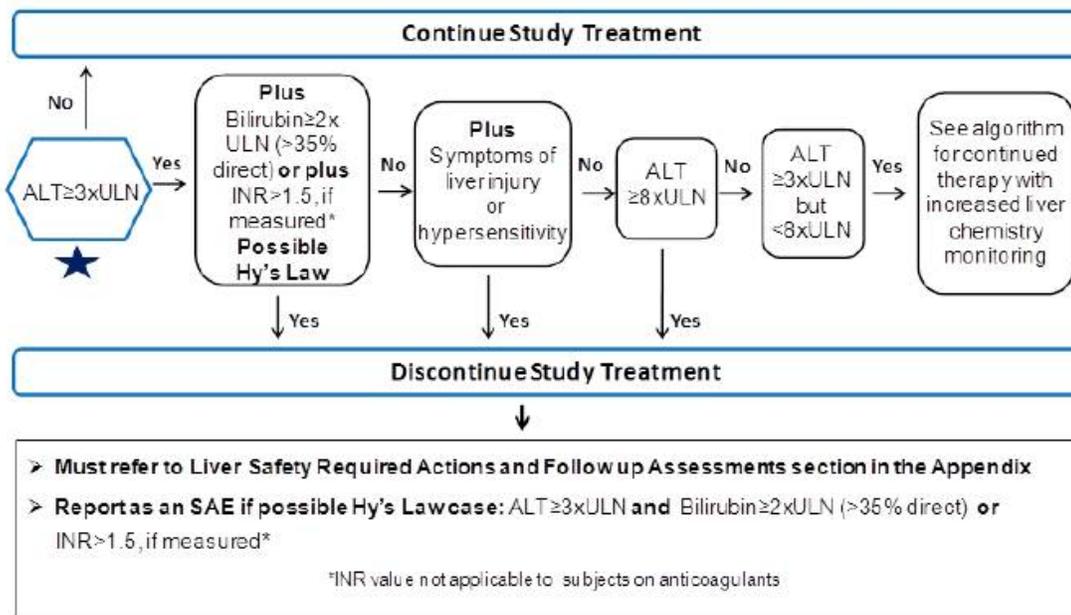
A set of criteria for **study discontinuation and follow-up investigation based on hepatic function test** (in reference to FDA premarketing clinical liver safety guidance) is specified herein to ensure the safety of subjects and to evaluate the causes of hepatic events. The guidelines related to this protocol are based on the FDA premarketing clinical liver safety guidance:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>.

The investigator should consider discontinuing the study treatment upon discovery of liver function test abnormal, and if the subject is applicable to any of the symptoms presented in the algorithm, or such discontinuation is determined to be the best choice for the subject as judged by the investigator.

Algorithm A: Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm

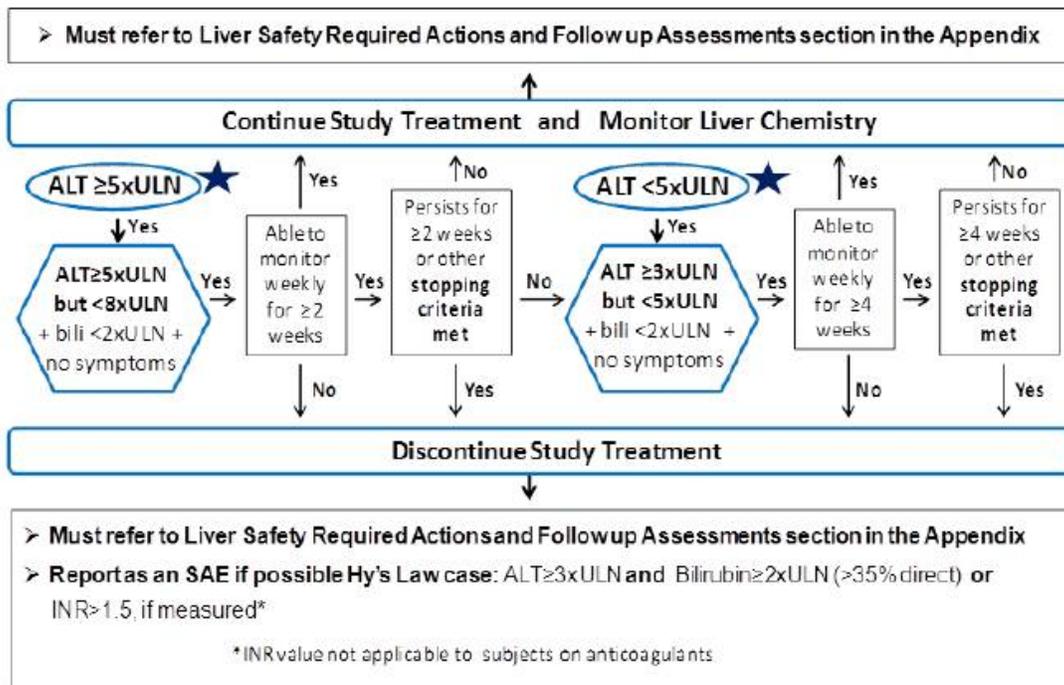
Algorithm A: Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

Algorithm B: Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT $\geq 3xULN$ but $< 8xULN$

Algorithm B: Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT $\geq 3xULN$ but $< 8xULN$



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

8.2.2. QTc Stopping Criteria

- For a decision on a subject's eligibility or study discontinuation, the same method for correction of QT interval must be used in the subject throughout the study, and must not be changed once the subject is enrolled.
 - For instance, if a subject is enrolled based on QTcB, decisions on the subject's withdrawal must be made based on QTcB.
 - The method used for correction of QT interval pertinent to the enrollment of a subject must be used for all QTc data to be collected throughout the study for the data analysis on the subject; provided that such rule is not applicable to ECG intended to ensure safety and also ECG not defined in the protocol.
- QTc should be determined based on a single measurement of ECG or the mean of ECG measured at 3 timepoints in a short period of time (e.g., 5 to 10 minutes). If abnormality is detected in a single measurement, ECG should be measured again, this time, at 3 timepoints.
- The lowest value of QTc cannot be used for a decision to withdraw a subject.

Refer to the schedule of assessment (SoA), completion visit (FV), for the details of data to be collected at the discontinuation of study treatment. Discontinue this study if the mean ECG is applicable to any of the following conditions:

- QTc >500 msec or uncorrected QT >600 msec
- Change in QTc from baseline >60 msec

The following withdrawal criteria should be applied for subjects with bundle branch block:

| Baseline for subjects with bundle branch block | Withdrawal criteria for subjects with bundle branch block |
|---|--|
| <450 msec | >500 msec |
| 450 to 480msec | IJYO530 msec |

8.2.3. Treatment discontinuation due to treatment-related SAE

A subject should be withdrawn from this study if treatment-related serious adverse event has occurred.

8.2.4. Treatment discontinuation due to pregnancy

A female subject who become pregnant during this study must be withdrawn from the study.

8.2.5. Withdrawal of subjects who start receiving prohibited medications or therapies

If a prohibited medication or therapy (See section 7.7.2.) needs to be started during the study, the subject must be withdrawn from this study; in which case, the subject must make the study completion visit (FV) before starting the prohibited medication or therapy.

8.2.6. Prohibition of treatment resumption

Study treatment must not be resumed in subjects who are once withdrawn from this study for a reason associated with hepatic function test, QTc, treatment-related serious adverse event, pregnancy, or commencement of a prohibited medication or therapy.

8.3. Lost to follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.

9.1. Efficacy assessments

9.1.1. Evaluation methods

9.1.1.1. Modified Ashworth Scale (MAS)

According to "2. SCHEDULE OF ACTIVITIES (SoA)" the investigator will use MAS (Table 5) to evaluate the level of spasticity. MAS should be measured and evaluated by the investigator, physiotherapist, or occupational therapist who has been given the training as an assessor.

The test should be performed on sitting position throughout the study. The affected parts should be extended as fast as possible to grade the flexor muscle tones. The final assessment will be made by the investigator in consideration of the information from physiotherapist or occupational therapist. The assessor should in principle remain unchanged throughout the study period.

Table 5 Modified Ashworth Scale (MAS)

| | |
|----|---|
| 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 ROM (range of movement) |
| 2 | More marked increase in muscle tone through most of the ROM, 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 measurement as inclusion criteria (Screening and Day 1)

The subject's wrist or fingers and elbow should all be evaluated as inclusion criteria. Subjects meeting the eligibility and randomized should be evaluated for MAS at Visit 1 of Treatment Period 1 on the same day; provided that measurement may be performed only once if the affected part to be evaluated is the same. The detail of inclusion criteria are shown in 6.1.

- MAS measurement during the blinded period

The subject's wrist, fingers, thumb and elbow should all be evaluated during the blinded period. Likewise, the subject's wrist, fingers, thumb and elbow should all be evaluated for MAS at Visit 5 and QRV of the blinded period. Subjects meeting the eligibility and transferred to the open-label period should be evaluated for MAS at Visit 1 of Treatment Period 2 on the same day; provided that measurement may be performed only once if the affected part to be evaluated is the same. Meanwhile, MAS needs to be evaluated again if the affected part to be evaluated is not the same. In subjects who have received no injection to any muscles affecting the thumb, MAS measurement on the thumb will not be performed.

- MAS measurement during the open-label period

During the open-label period, MAS should be evaluated for the flexors at which the muscle given the study treatment functions (fingers, thumb, wrist, elbow, fore-arm) (Table 6). If the subject is determined to be eligible, the V5/QRV and V1 would be on the same day, and therefore, the MAS

measured at V5/QRV of the previous treatment period should not be measured again on V1; the measurement on V5/QRV should be used for the assessment (Figure 6). MAS on flexors to be newly assessed on V1 should be evaluated before dose on V1. The MAS on the shoulder should be evaluated comprehensively for the adductor and invertor.

Table 6 Regions to be evaluated for MAS during the open-label period

| Number | Muscles to be injected | Regions to be evaluated for MAS |
|--------|--------------------------------|--|
| A1 | Biceps brachii | Elbow flexors (flexion) |
| A2 | Brachialis | |
| A3 | Brachioradialis | |
| B1 | Flexor carpi radialis | Wrist flexors (flexion) |
| B2 | Flexor carpi ulnaris | |
| C1 | Flexor digitorum profundus | Fingers (flexion) |
| C2 | Flexor digitorum superficialis | |
| C3 | Lumbricales interossei | |
| D1 | Flexor pollicis longus | Thumb (flexion, adduction) |
| D2 | Adductor pollicis | |
| D3 | Opponens pollicis | |
| E1 | Pronator teres | Forearm (pronate) |
| E2 | Pronator quadratus | |
| F1 | Teres major | Shoulder (flexion, adduction, and internal rotation) |
| F2 | Latissimus dorsi | |
| F3 | Pectoralis major | |
| F4 | Subscapularis | |

| Visit | SV | Part 1 | | | | | Part 2 | | | | | Part 3 | | | | | Part 4 | | | | | |
|------------|----|--------|----|----|----|----|--------|----|----|----|----|--------|----|----|----|----|--------|-----|----|----|----|---|
| | | V1 | V2 | V3 | V4 | V5 | V1 | V2 | V3 | V4 | V5 | V1 | V2 | V3 | V4 | V5 | V1 | V2 | V3 | V4 | V5 | |
| A.Elbow | ● | ● | ● | ● | ● | ● | (○) | ● | ● | ● | ● | (○) | ● | ● | ● | ● | (○) | ● | ● | ● | ● | ● |
| B.Wrist | ● | ● | ● | ● | ● | ● | | | | | | | ● | ● | ● | ● | ● | (○) | ● | ● | ● | ● |
| C.Finger | ● | ● | ● | ● | ● | ● | (○) | ● | ● | ● | ● | (○) | ● | ● | ● | ● | (○) | ● | ● | ● | ● | ● |
| D.Thumb | | ● | ● | ● | ● | ● | | | | | | | | | | | | | | | | |
| E.Forearm | | | | | | | ● | ● | ● | ● | ● | (○) | ● | ● | ● | ● | (○) | ● | ● | ● | ● | ● |
| F.Shoulder | | | | | | | ● | ● | ● | ● | ● | | | | | | ● | ● | ● | ● | ● | ● |

● : MAS measurement (before treatment)
 (○) : Use V5 or QRV MAS measurement

Figure 6 Subjects to be evaluated for MAS

9.1.1.2. Numeric Rating Scale (NRS)

According to "2. SCHEDULE OF ACTIVITIES (SoA)" the investigator (or subinvestigator) will use NRS (Figure 7) to evaluate the severity of flexors pain.

The investigator will perform the interview on NRS following the assessment of MAS. Each subject will be interviewed on the severity of pain on the treated part when extended based on a scale with 0

being "no pain" and 10 being "the worst imaginable pain"; 1 response on the scale should be selected by the subject.

| | | | | | | | | | | |
|---------|---|---|---|---|---|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| No pain | | | | | | | | | | Pain as bad as you can imagine |

Figure 7 Numeric Rating Scale (NRS) for pain

- NRS measurement during the blinded period

During the blinded period, the severity of pain in the elbow flexors will be evaluated.

- NRS measurement during the open-label period

During the open-label period, a major part with pain [specify 1 part from among fingers, thumb, wrist, elbow, fore-arm (pronate), and shoulder] will be evaluated for the severity of pain on Visit 1. The part to be evaluated does not have to be the same within each treatment period, but should be the same part as that evaluated for MAS.

9.1.1.3. Disability Assessment Scale (DAS)

According to "2. SCHEDULE OF ACTIVITIES (SoA)" the investigator (or subinvestigator) will use the 4 disability assessment parameters presented in Table 7 and evaluate all of them based on the scale presented in Table 8. Before starting the study treatment, the investigator shall discuss with the subject, and select and evaluate 1 parameter agreed with the subject as the "main assessment parameter." The assessor should in principle remain unchanged throughout the study period. The main assessment parameter should also remain unchanged throughout the study period.

Table 7 Disability assessment parameters

| | Content of assessment |
|--------------|--|
| Hygiene | The extent of maceration/ulceration and/or palmar infection, palm/hand cleanliness, ease of cleanliness, ease of nail trimming, and interference with hygiene-related disability in the subject's daily life |
| Pain | The intensity of pain/discomfort, and the interference that upper-limb pain-related disability has in the patient's daily life. |
| Dressing | The difficulty or ease for the subject in putting on the relevant clothing (e.g., shirts, jackets, gloves, etc.) and the interference that upper-limb dressing-related disability has in the patient's daily life. |
| Limb posture | The psychological and/or social interference that the disfigured upper limb has in the patient's daily life. |

Table 8 Disability Assessment Scale

| | Description |
|-----------------------------|--|
| 0: No functional disability | No functional disability |
| 1: Mild disability | Noticeable but does not interfere significantly with normal activities |
| 2: Moderate disability | Normal activities require increased effort and/or assistance. |
| 3: Severe disability | Normal activities limited. |

9.1.1.4. Clinical Global Impression of Change (CGI) assessed by an investigator

The investigator (or subinvestigator) will evaluate CGI according to "2. SCHEDULE OF ACTIVITIES (SoA)"; Changes in spasticity (Clinical Global Impression) from baseline (V1 in each treatment phase) will be evaluated by 9 grades as shown in Table 9.

The investigator shall also consider the subject's clinical symptoms and adverse events pertinent to the assessment of CGI. Also, the therapeutic effect of the product injected in the subject's fingers, wrist, and elbow should be taken into an account. The assessor should in principle remain unchanged throughout the study period.

Table 9 Clinical Global Impression of Change (CGI)

| | |
|----|---------------------|
| -4 | Very much worsened |
| -3 | Much worsened |
| -2 | Moderately worsened |
| -1 | Slightly worsened |
| 0 | Unchanged |
| +1 | Slightly improved |
| +2 | Moderately improved |
| +3 | Much improved |
| +4 | Very much improved |

9.1.1.5. Clinical Global Impression of Change (CGI) assessed by a patient

According to "2. SCHEDULE OF ACTIVITIES (SoA)" the investigator (or subinvestigator) will use Table 9 to record subject-reported CGI. The investigator shall interview each subject on changes in spasticity from predose, and the subject will evaluate it using Table 9.

9.1.1.6. Time to patient-reported onset of spasticity symptom relief (Visit 2):

According to "2. SCHEDULE OF ACTIVITIES (SoA)" the investigator (or subinvestigator) will record the time to alleviation of spasticity reported by subjects. The investigator shall ask the subject whether the product was effective on the spasticity, and if the subject's response to the question is positive, ask him/her "how many days did it take for the therapeutic effect to appear after the current dose?" and record the number of days.

9.1.1.7. Patient-reported benefit of injection (Visits 3, 4, and 5)

According to "2. SCHEDULE OF ACTIVITIES (SoA)" the investigator (or subinvestigator) will record the efficacy of treatment reported by subjects. The investigator shall ask, "Was the product effective?" and the subject shall respond either by "Yes" or "No."

9.2. Adverse events

Definitions of adverse events and serious adverse events (SAE) are as specified in Appendix 4. The investigator or a person assigned by the investigator is responsible for detecting, recording, and reporting events that match the definitions of adverse events and SAEs, and also, responsible for follow-up investigations on SAEs, as well as events related to the study drug or this study, and events that resulted in treatment discontinuation or subject withdrawal (See section 8).

9.2.1. Period subject to collection of data related to adverse events and SAEs, and the frequency of such data collection

- All SAEs will be collected from the start of treatment until Final Visit at the time points specified in the SoA (Section 2).
- All AEs will be collected from the start of treatment until Final Visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method used to detect adverse events and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.2.3. Follow up on adverse events and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory requirements of SAE reporting

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Cardiovascular events and death

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

9.2.6. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study treatment and until Final Visit.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix [X].
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.3. Management of overdose

A dosage of the product exceeding 400 units within 24 hours shall be considered as overdose in this study. Overdose may cause excessive pharmacodynamic responses such as hyposthenia, muscular paralysis, and other localized adverse reactions. Symptoms and signs may not immediately appear following dose. Moreover, blepharoptosis, dysarthria, dysphagia, dyspnea, myasthenia, and other events suspected to be an effect on other muscles distal to the treated muscle have been reported overseas. If such a symptom appears, the subject should be carefully monitored, and given appropriate interventions, if necessary with hospitalization. Also, supportive therapies such as artificial breathing should be considered for respiratory symptoms.

Upon confirmation of overdosage, the investigator should;

1. Contact the Medical Monitor immediately.

Carefully monitor the adverse event/SAE, and laboratory abnormalities in the subject for at least 4 weeks; and

Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

The investigator shall discuss with the sponsor's medical monitor on the clinical assessment of the subject, and upon which, decide whether or not to discontinue the study treatment.

9.4. Safety assessments

Assessment timepoints for all safety parameters are as shown in SoA.

9.4.1. Physical examination

Physical examination (complete version): Only during screening

- The head and neck, skin, lungs, cardiovascular system, abdominal region (liver and spleen), gastrointestinal system, lymph node, and nervous system should be examined, and the results thereof should be recorded; these organs should be examined for the presence/absence of pre-existing conditions and abnormal findings, and if there is any suspected abnormality, detailed examinations should be performed.
- The pulmonary function test should be conducted in details if any sign of pulmonary impairment is found. For the pulmonary function test, spirometry by pulmonologists is recommended.

Physical examination (simplified version): To be conducted only if an eligibility criterion is not met during the open-label period.

- At least, the lungs, cardiovascular system, and abdominal region (liver and spleen) should be examined, and the results thereof should be recorded.
- The investigator should pay attention to clinical signs and symptoms related to a history of serious disease.

The physical examinations should be performed by doctors in accordance with the standard clinical guidelines of each study site.

9.4.2. Vital signs

- For the vital signs, body temperatures (oral, intra-aural, or axillary fossa), systolic/diastolic blood pressures, and pulse rates should be measured in a semi-recumbent position after a 5-minute rest. If measurement in a semi-recumbent position is difficult, measurement in another position (e.g., sitting) is acceptable. In this case, however, the measurement should be performed always in the same position during the study period.
- If a temperature is to be measured orally, the subject must refrain from eating food or drinking beverage within 5 minutes before the measurement. The method for the measurement of body temperature must remain the same throughout the study.

- The blood pressures and pulse rates should be measured with an automated device. A manual method may be used only if there is no automated device available for use.

9.4.3. Height and weight

The standard clinical guidelines of each study site should be followed.

9.4.4. Pulmonary test

- Refer to SoA for the timepoints and frequency of testing.
- If post-injection SpO₂ is decreased by 3% or more from the baseline (pre-injection on Day 1) or a SpO₂ value is <95%, medical examination by pulmonologist is required. A subject with pulmonary dysfunction due to study treatment based on the investigator's opinion will be referred to a pulmonologist as well.
- If a medical institution has no pulmonologist, visit other hospitals for medical examination by specialists. For the pulmonary function test, spirometry by pulmonologists is recommended.
- If a subject is referred to a pulmonologist and considered to have no concerns about pulmonary function, the investigator should carefully consider whether to start or continue study treatment.

9.4.5. ECG

- QTc should be determined based on a single measurement of ECG or the mean of ECG measured at 3 timepoints in a short period of time (e.g., 5 to 10 minutes).
- An automated measurement and manual re-interpretation in accordance with SoA should be used to collect data on the heart rates, PR, QRS, QT, and QTc interval. Refer to section [8.2.2.](#) for QTc-related treatment discontinuation standard, and additional QTc to be measured as required.
- Each interval between timepoints for the measurement of ECG should be minimized as much possible (within 2 minutes). The measurement of ECG should be performed 3 times consecutively and completed within 5 to 10 minutes.

9.4.6. Neutralizing antibody test

The investigator shall draw blood for neutralizing antibody samples in accordance with the study schedule. The neutralizing antibody will be measured collectively by central laboratories designated by GSK (Intertek Pharmaceutical Services Co. and Pacific BioLabs Co.). The screening samples will be retained temporarily by the central laboratories, and then, upon retrieval of samples from all subjects, will be collected and tested by Intertek for screening. Samples tested positive at Intertek will be separately sent to Pacific BioLabs for retest to finalize the results of neutralizing antibody test. The above procedures shall also be taken for samples collected for Week 12 visit during the blinded period, and upon completion of study treatment in all subjects.

9.4.7. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory parameters that should be tested, and to SoA for the timepoints and frequency of testing.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If a result of clinical laboratory test not scheduled in the protocol is obtained by a study site, which requires a change in the patient management, or is determined to be clinically important by the investigator, that is SAE, adverse event, an event requiring dose modification, or any other relevant event, the record thereof must be documented in the CRF.
- Follow-up investigation may be performed at any time during the study as determined to be necessary by the investigator, or required by the Japanese regulation.

9.5. Pharmacokinetics

PK parameters are not evaluated in this study.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics/Pharmacogenetics

Genetics and pharmacogenetics are not evaluated in this study.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

9.9. Pharmacoeconomics

Pharmacoeconomic parameters are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

This study is not intended to verify a statistical hypothesis, but is rather intended to verify that the responder rate in the 400 units group exceeds that in the 240 units group, and for which, about 120 subjects (60 in each treatment group) are to be enrolled.

During Treatment Period 1 of this study, 160 units of the product will be administered in the muscle which affects the elbow; thus, the sample size was determined in reference to an overseas phase III study (Study 127) in which a similar dosage as this study (150 units) was administered in the muscle which affects the elbow. The responder rate in the elbow at Week 6 of the initial dose in Study 127 was 72.2% and 47.1% in the product 300 units group (150 units in the muscle which affects the elbow flexors) and placebo group, respectively. The number of subjects in the intention-to-treat (ITT) population was small in both the product 300 units group and placebo group of Study 127, which was 18 subjects each; thus, considering the uncertainty of the results of Study 127, the responder rates in the product 400 units and 240 units groups in this study were conservatively assumed to be 70.0% and 50.0%, respectively. Assuming that the sample size is 60 subjects in each group, the power of test to detect an intergroup difference in the responder rates would be about 62% with a two-sided significance level of 5% while the probability of the responder rate in the product 400 units group to exceed that in the product 240 units group as a point-estimate would be $\geq 98\%$.

With about 120 subjects enrolled, 100 subjects are expected to complete Week 48 of the initial dose.

10.2. Populations for Analyses

Populations for statistical analyses in this study are defined as follows.

| Population | Description |
|------------|--|
| ITT | All subjects randomized in the study and had at least 1 post-baseline efficacy assessment: ITT is the primary efficacy analysis population, and the subjects will be analyzed in line with the randomized treatment group. |
| Safety | All subjects randomized in the study and received study treatment at least once: The subjects will be analyzed based on the treatment actually given. |

10.3. Statistical Analyses

10.3.1. Efficacy Analyses

This study is not intended to verify a statistical hypothesis; thus, there will be no statistical test.

All of the efficacy analyses will be performed on the ITT population separately for the blinded period and the open-label period.

| Endpoints | Statistical Analysis Methods |
|-------------|---|
| Primary | <p>The primary endpoint is the proportion of subjects whose MAS score on the elbow at Week 6 of the initial dose decreased by at least 1 level from the baseline (responder rate). The primary endpoint will be calculated as the proportion of subjects whose MAS score decreased by at least 1 level from the baseline in the ITT population. Also, a 95% confidence interval of the intergroup difference in the responder rate will be computed. Subjects with no MAS score available at Week 6 will not be counted as subjects whose MAS score decreased by at least 1 level from the baseline (that is, counted in as non-responder).</p> <p>The MAS scores, 0, 1, 1+, 2, 3, and 4 will be encoded to 0, 1, 2, 3, 4, and 5, respectively, for the analysis purpose.</p> |
| Secondary | <p>Unless specified otherwise, the data up to Week 12 of treatment will be summarized for each repeated dose during the open-label period.</p> <p>During the blinded period, a mixed model for repeated measurement (MMRM) will be used for the analysis on the endpoints specified below, and the least-square mean and 95% confidence interval will be calculated. The details of the model will be described in the statistical analysis plan. For the open-label period, only a summary statistics will be performed for each treatment group. Missing values will not be imputed.</p> <ul style="list-style-type: none"> · Change in MAS score in the fingers, thumb, wrist, and elbow from the baseline · Change in Disability Assessment Scale (primary endpoint) from the baseline <p>The proportion of subjects in whom MAS score in the fingers, thumb, wrist, and elbow decreased by at least 1 level from the baseline (responder rate) during the blinded period will be analyzed with the same method as that for the primary endpoint. For the open-label period, the denominator to be used for the calculation of responder rate shall be the number of subjects in each subgroup stratified by the number of injections given, not the ITT population. Also, a 95% confidence interval of the intergroup difference in the responder rate will not be calculated.</p> |
| Exploratory | <p>Time to patient-reported onset of spasticity symptom relief will be evaluated for subjects who reported alleviation of spasticity at in 2 weeks postdose. The number of days from dose to the alleviation of spasticity will be summarized for each treatment group.</p> <p>Clinical Global Impression of Change (CGI) assessed by an investigator, CGI assessed by a patient, and Patient-reported benefit of injection will be summarized for each treatment group. Missing values will not be complemented.</p> <p>Other details will be specified in the statistical analysis plan.</p> |

10.3.2. Safety Analysis

Safety analyses will all be performed on the safety population separately for the blinded and open-label periods.

| Endpoints | Statistical Analysis Method |
|-------------|---|
| Primary | Not applicable |
| Secondary | Adverse events that occurred in the overall study period, blinded period, and open-label period will be summarized for each treatment group. For the blinded period, 2 patterns of analyses on adverse events will be performed; one is on adverse events that occurred between the initial dose and the first dose in the open-label period (or at the completion of study if no dose is given in the open-label period or at the study withdrawal), and another one is on adverse events that occurred within 84 days from the initial dose. Adverse events will be summarized separately for SOC (system organ class) and PT (preferred term). Also, adverse events related to study treatment, adverse events that resulted in discontinuation, adverse events by subgroups stratified by severity, and serious adverse events will be summarized. Laboratory findings and vital signs at each visit and their changes from baseline will be summarized for each treatment group. |
| Exploratory | Will be specified in the statistical analysis plan. |

10.3.3. Other analyses

Other analyses will be specified in the statistical analysis plan.

10.3.4. Interim analyses

The details of the interim analysis plan will be specified in the statistical analysis plan.

When all subjects (except for early termination) complete the visit at Week 24 of the initial dose, the data on all of the subjects until Week 24 of the initial dose may be locked, unblinded, and analyzed for reporting to authorities.

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12. Appendices

12.1. Appendix 1: Abbreviations and trademarks

Trademark

| Trademark of Glaxo SmithKline Group | Trademarks that do not belong to Glaxo SmithKline Group |
|-------------------------------------|---|
| Botox | — |

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in [Table 10](#) will be performed by central laboratory.
- A test needs to be performed by study sites only if the result cannot be obtained from the central laboratory in time for study treatment and/or assessment. Even if measurement is performed at a study site, another sample at the same assessment timepoint is separately required for measurement at central laboratory. If a result of measurement at the study site is to be used for a decision of study treatment and/or assessment, the result should be recorded in the CRF.
- Protocol-specific inclusion/exclusion criteria are as specified in section 6 of the protocol.
- Protocol-specific inclusion/exclusion criteria are as specified in section 6 of the protocol.

Table 10 Protocol-Required Safety Laboratory Assessments

| Clinical laboratory | Parameters | | | |
|--|--|----------------------|--|---|
| Hematological tests | Platelet count | | Erythrocyte indices: | Percentage of white blood cell: Neutrophil Lymphocyte Monocyte Eosinophil Basophil |
| | RBC | | Mean corpuscular volume (MCV) | |
| | Hemoglobin | | Mean corpuscular hemoglobin (MCH) | |
| | Hematocrit | | Reticulocyte count (%) | |
| | White blood cell count | | | |
| Chemistry ¹ | Urea nitrogen (BUN) | Potassium | Aspartate aminotransferase (AST) / Serum glutamic oxaloacetic transaminase (SGOT) ¹ | Total bilirubin and direct bilirubin |
| | Creatinine | Sodium | Alanine aminotransferase (ALT) / Serum glutamic pyruvic transaminase (SGPT) ¹ | Total protein |
| | Calcium | Alkaline phosphatase | | |
| Urinalysis | Specific gravity PH with test paper, glucose, protein, occult blood, ketone, bilirubin, urobilinogen, nitrite, and white blood cell esterase Microscopy (if occult blood or protein is deviated) | | | |
| Other tests | <ul style="list-style-type: none"> Pregnancy test (if necessary in a woman of child-bearing potential): Serum or urine human chorionic gonadotropin (hCG)² <p>The following parameters should be tested during the screening period.</p> <ul style="list-style-type: none"> Serological verification: HIV antibody The following parameters should be tested only for subjects with chronic hepatitis B or C that is stabilized at screening, and subjects currently receiving or expected to receive immunosuppressant. <ul style="list-style-type: none"> Serological verification: Hepatitis B virus surface antigen (HBsAg), and hepatitis C virus antibody The following parameter should be tested for women of no child-bearing potential. <ul style="list-style-type: none"> Follicle stimulating hormone and estradiol | | | |
| Caution: 1. Details of the discontinuation criteria based on hepatic function test, and the interventions and follow up necessary after the occurrence of hepatic events are specified in section 8.1 and Appendix 6. SAEs must be reported for all events with ALT IJYO3 times the upper limit of normal range (ULN), and at the same time, bilirubin IJYO2 times the ULN (direct bilirubin >35%), or ALT IJYO3 times the ULN, and at the same time, the international normalized ratio (INR) >1.5 if measured [which suggests a possibility of severe liver injury (applicable to Hy's Law)]. 2. Pregnancy tests should be performed with serum samples at screening, and with urine samples for routine tests after randomization. | | | | |

12.3. APPENDIX 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
 - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
 - Applicable ICH Good Clinical Practice (GCP) Guidelines
 - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
 - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
 - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
 - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Process of obtaining consent

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Data protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Composition of committee

No committee will be established.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- Disclosure of a Clinical Study Report (CSR) after the evaluation by the regulatory authority(ies).
- GSK may post the study information and tabulated-form study results on the website (www.ClinTrials.gov) of the U.S. National Institution of Health (NIH) or other websites open to the public
- GSK may post the study results to scientific journals that conduct peer review in order to report the study results.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the corresponding list of source documents.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.4. APPENDIX 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of an SAE

If an event does not correspond any of the above definitions of an AE, even if it is a serious condition, it will not be regarded as an SAE (e.g.; hospitalization due to the signs/symptoms of the disease being studied, death caused by exacerbation of the disease).

A SAE is defined as any untoward medical occurrence that, at any dose:**a. results in death****b. is life-threatening**

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. requires hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the investigator's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. is congenital anomaly/birth defect

f. other important medical situations:

- Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/angina unstable
- Cardiac failure congestive
- Arrhythmia
- Valvular disease
- Pulmonary hypertension
- Cerebrovascular event/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep vein thrombosis/pulmonary embolism
- Revascularisation

Recording of AEs and SAEs**AE and SAE Recording**

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and classify it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities - An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as “serious”, not when it is assessed as severe but when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of causality

- The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE.
- A “reasonable possibility” is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgement to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated.
- The investigator will also consult the IB, for marketed products, in the determination of his/her assessment.
- The investigator must record that he or she reviewed AEs and SAEs and assessed the causality in the medical record.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, prepare and send the follow-up report of SAE by amending the assessment result of the causality accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit all updated SAE data to GSK within 24 hours after obtaining the information.

Reporting of SAEs to GSK**SAE Reporting to GSK via Electronic Data Collection Tool**

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the SAE coordinator by telephone.
- Contacts for SAE reporting can be found in ATTACHMENT.

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE page of the CRF is the preferred method to transmit the information on SAEs to GSK.
- In rare circumstances and in the absence of facsimile equipment, initial notification by telephone is acceptable followed by a copy of the SAE page of the CRF sent by overnight mail or by courier.
- Initial notification via the telephone does not replace the need for the investigator (or subinvestigator) to complete and sign the SAE page of the CRF within the designated reporting time frames.
- The ATTACHMENT 1 shows a contact information to which the SAEs should be reported.

12.5. APPENDIX 5: Contraceptive Guidance and Collection of Pregnancy Information

Definition

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP

1. Premenarchal

Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

Postmenopausal women

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male study subject

- A male study subject who has a female partner of childbearing potential can participate in this study if he agrees to any of the following conditions:
- He must agree not to have a sex (sexual intercourse) with a person of the opposite sex as a normal favourable lifestyle (continuously having no sex for a long period of time) and also agree to keep that condition.
- If he has a sex with a woman of childbearing potential, he must agree to use a male condom and use at least one of the contraception methods with an annual failure rate below 1% which are shown in Table 11.
- A male study subject who has a pregnant or breastfeeding female partner must agree not to have a sex from the time during the study or use a male condom when having a sex.
- A male study subject must agree not to provide his sperm during the study.

Female study subject

A female study subject of childbearing potential can participate in this study if she agrees to use any of the extremely effective methods of contraception shown in Table 11 continuously and accurately. Among the methods of contraception shown in Table 11, those deleted with strikethrough lines have neither been approved nor been accepted in Japan.

Table 11 Extremely effective methods of contraception

| |
|---|
| User-dependent extremely effective methods of contraception ^a Their annual failure rates are below 1% if they are used continuously and accurately. |
| Contraception by mixed (estrogen and progestogen-containing) hormone preparation (inhibit ovulation) ^b <ul style="list-style-type: none"> • Oral • Intravaginal • Transdermal |
| Contraception by only progestogen-containing hormone preparation (inhibit ovulation) ^b <ul style="list-style-type: none"> • Injection |
| User-independent extremely effective methods of contraception |
| <ul style="list-style-type: none"> • Contraception by only progestogen-containing implantable hormone preparation (inhibit ovulation)^b • Intrauterine device (IUD) • Intrauterine system (IUS) • Bilateral tubal occlusion |
| Male partner's vasectomy (If her male partner has been vasectomised, it is an extremely effective method of contraception for a woman of childbearing potential if that partner is the only man with whom she has a sex and it has been confirmed that he is sterile. Otherwise, he/she must use other additional extremely effective method(s) of contraception.) |
| Having no sexual relations (If the subjects decide to refrain himself or herself from having a sex of the opposite sex for the entire period when there is a risk of the investigational product, abstinence is deemed to be an extremely effective method of contraception. However, the credibility of abstinence needs to be evaluated during the study period and from the perspectives of the subject's normal favourable lifestyle.) |

Notes:

- a. The usual failure rate is different from the rate when contraception is used continuously and accurately. The subjects should use the methods of contraception that match with regulations concerning the methods of contraception for study subjects in each country.
- b. The efficacy of contraception by hormone preparations may decrease as a result of the interaction with the investigational product. In that case, the subject should use two extremely effective methods of contraception during the treatment period and at least for 3 months after the last dose of the investigational product.

Pregnancy test

- A woman of childbearing potential can be enrolled to this study only if it is confirmed that she is negative in a highly sensitive serum pregnancy test along with her menstrual period.
- Pregnancy test should be performed if no menstruation occurred or she is suspected to be pregnant.
- Analysis should be performed according to the package insert using a testing kit provided by GSK.

Collection of pregnancy information**If a male study subject's partner becomes pregnant**

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

For a female study subject who discovers her pregnancy while participating in this study,

- The administration of the investigational product will be discontinued.

12.6. APPENDIX 6: Liver Safety Required Actions and Follow up Assessments

In order to secure the subject's safety and evaluate the causes of liver event, **the criteria for discontinuation and follow-up based on the liver function test values in the phase III-IV studies** will be stipulated.

Criteria for discontinuation based on the liver function test values in the phase III-IV studies and necessary follow-up

| Criteria for discontinuation based on the liver function test values | |
|---|--|
| ALT | ALT \geq 8xULN |
| ALT increase | ALT \geq 5xULN but <8xULN persists for \geq 2 weeks ALT \geq 3xULN but <5xULN persists for \geq 4 weeks |
| Bilirubin ^{1,2} | ALT \geq 3xULN and bilirubin \geq 2xULN (>35% direct bilirubin) |
| INR ² | ALT \geq 3xULN and INR>1.5, if INR measured |
| Cannot Monitor | ALT \geq 5xULN but <8xULN and cannot be monitored weekly for \geq 2 weeks ALT \geq 3xULN but <5xULN and cannot be monitored weekly for \geq 4 weeks |
| Symptom ³ | ALT \geq 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity |
| Necessary measures and assessment items for liver event | |
| Actions | Follow Up Assessments |
| <ul style="list-style-type: none"> Immediately discontinue the administration of the investigational product. Report it to GSK within 24 hours. Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE². Perform liver event follow up assessments Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below) Do not restart/rechallenge participant with study treatment unless allowed per protocol and GSK Medical Governance approval is granted If the resumption/re-administration of the investigational product is not stipulated in the protocol or approved by GSK's Medical Governance, the administration of the investigational product will be discontinued | <ul style="list-style-type: none"> Viral hepatitis serology⁴ Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend Only in those with underlying chronic Hepatitis B at study entry (identified by positive Hepatitis B surface antigen) quantitative Hepatitis B DNA and Hepatitis delta antibody⁵ Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). Fractionate bilirubin, if total bilirubin \geq 2xULN Obtain complete blood count with differential to assess eosinophilia Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. |

| | |
|--|--|
| <p>permanently and the follow-up prescribed in the protocol 8.1. will be conducted.</p> <p>MONITORING:</p> <p><u>For bilirubin or INR criteria:</u></p> <ul style="list-style-type: none"> • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended <p><u>For other criteria:</u></p> <ul style="list-style-type: none"> • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72 hrs • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline | <ul style="list-style-type: none"> • Record alcohol use on the liver event alcohol intake case report form (CRF) page <p><u>For bilirubin or INR criteria:</u></p> <ul style="list-style-type: none"> • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms. |
|--|--|

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT $\geq 3xULN$ and bilirubin $\geq 2xULN$. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.

All events of ALT $\geq 3xULN$ and bilirubin $\geq 2xULN$ (>35% direct bilirubin) or ALT $\geq 3xULN$ and INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)

Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen (HbsAg) and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody

Criteria for follow-up with continued treatment based on the liver function test values in the phase III-IV studies

| Criteria for follow-up based on liver test function values – Liver events to be followed | |
|---|---|
| Criteria | Actions |
| <p>ALT \geq5xULN and <8xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 2 weeks.</p> <p>OR</p> <p>ALT \geq3xULN and <5xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks.</p> | <ul style="list-style-type: none"> • Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT \geq5xULN and <8xULN to \geq3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline. |

12.7. APPENDIX 7: COUNTRY SPECIFIC DESCRIPTIONS

12.7.1. Regulatory and Ethical Considerations

This study will be conducted in compliance with the “Good Clinical Practice (GCP)” (MHW Ordinance No. 28, March 27, 1997) and the “Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, etc. (PMD Act)”.

GSK will submit the CTN to the regulatory authorities in accordance with the PMD Act before concluding the study agreement with the medical institution

12.7.2. Obtaining of Informed Consent

Prior to participation in the study, the investigator should fully inform the potential subject and/or his or her legally acceptable representative of the study using the information document. In doing so, the investigator should provide the subject sufficient time and opportunity to inquire about details of the study and obtain the subject and/or his or her legally acceptable representative’s signature or printed name and seal and date of consent on the consent form. The subject may take the informed consent form home to review it. The person who provided the explanation and the clinical research coordinator who provided the supplementary explanation should also sign or affix his or her printed name and seal on the consent form and enter the date of signature. If an impartial witness is needed, he or she should also sign or affix his or her printed name and seal on the consent form and enter the date of witness. The investigator should attach the original of the above signed or affixed with printed name/seal and dated consent form (and information document) to the original medical record such as medical chart (in accordance with the rules for records retention, if any, at each medical institution), retain it, and give a copy to the subject and/or his or her legally acceptable representative.

12.7.3. Study Implementation Period

July 2017 – February 2019

12.7.4. Study Conduct Structure

The Attachment 1 shows the sponsor’s information. Also, the Attachment 2 shows a list of medical institutions and investigators.

12.8. APPENDIX 8: PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

The protocol amendment summary of changes table for the latest amendment is provided on the pages before the contents.

Amendment 1: 24-MAY-2017

Overall Rationale for the Amendment:01

The protocol was changed based on the regulatory inquires by the Pharmaceuticals and Medical Devices Agency (PMDA).

Overall Rationale for the Amendment: 01

| Section # and Name | Description of Change | Brief Rationale |
|--------------------|-----------------------|-----------------|
|--------------------|-----------------------|-----------------|

| Section # and Name | Description of Change | Brief Rationale |
|---|---|--|
| 1. SYNOPSIS | Add pulmonary test and description adjustment | Requested by PMDA |
| 2. SCHEDULE OF ACTIVITIES (SoA) | Add pulmonary test and description adjustment | Requested by PMDA |
| 5.1.3.1. Eligibility Criteria for Injection in and after Part 2 | Add pulmonary test | Requested by PMDA |
| 6.1.1. Screening Phase (Day -28 to Day -1) | Add pulmonary test | Requested by PMDA |
| 6.2.2. Day 1 (Prior to injection) | Description adjustment | Establish consistency with section 7.7.2 |
| 6.4. Screen Failures | Description adjustment | Not shown due to minor changes |
| 7.7.2. Contraindicated Medications/Therapies | Description adjustment | Establish consistency with section 6.2.2 |
| 9.1.1.4. Clinical Global Impression of Change (CGI) assessed by an investigator | Error correction | Not shown due to minor changes |
| 9.4.4. Pulmonary test | Add pulmonary test | Requested by PMDA |
| 9.4.5.ECG | Description adjustment | Add manual re-interpretation |

Amendment 2: 6-OCT-2017

Overall Rationale for the Amendment: 02

The protocol was revised for study procedure clarification, error correction, and description adjustment.

| Section # and Name | Description of Change | Brief Rationale |
|--|---|--|
| Cover | Change of address | Office relocation |
| 1. SYNOPSIS, | Delete laboratory data from the Eligibility Criteria for Injection in and after Part 2. Add eligibility criteria regarding the pulmonary test. | GSK1358820 is unlikely to affect laboratory test data. Specify the acceptable range of SpO ₂ values. |
| 2. SCHEDULE OF ACTIVITIES (SoA) | Add a footnote. | Clarify the procedure for V1 assessment in and after Part 2. |
| 5.1.3.1. Eligibility Criteria for Injection in and | Delete laboratory data from the Eligibility Criteria for Injection in and after Part 2. | GSK1358820 is unlikely to affect laboratory test data. |

| Section # and Name | Description of Change | Brief Rationale |
|---|--|--|
| after Part 2 | Add eligibility criteria regarding the pulmonary test. | Specify the acceptable range of SpO ₂ values. |
| 6.2.2. Day 1 (Prior to injection) | Add eligibility criteria regarding the pulmonary test. | Specify the acceptable range of SpO ₂ values to ensure the safety. |
| 7.1. Treatments Administered Table 2. Muscle Involvement and Dose in the Blind Phase Table 3. Muscle Involvement and Reference Dose in the Open-Label Phase | Description adjustment | Not shown due to minor changes. |
| 7.7.1. Permitted Concomitant Drugs/Therapies | Description adjustment | Delete tolperisone hydrochloride, which has been withdrawn from the market. |
| 7.7.1. Permitted Concomitant Drugs/Therapies | Add a description regarding rehabilitation therapies. | Specify acceptable rehabilitation therapies and the procedure for collecting rehabilitation therapy related information. |
| 9.1.1.1. Modified Ashworth Scale (MAS) | Description adjustment | Add a description regarding MAS assessment on the thumb. |
| 9.1.1.1. Modified Ashworth Scale (MAS) Table 6. Regions to be evaluated for MAS during the open-label period | Description adjustment | Not shown due to minor changes |
| 9.4.2. Vital signs | Add a description regarding measurement in a sitting position. | Add an instruction for vital sign measurement. |
| 9.4.4. Pulmonary Test | Add a description regarding the pulmonary test. | Specify the acceptable range of SpO ₂ values to ensure the safety. |