STUDY PROTOCOL

A double-blind, randomised, placebo controlled, proof-of-concept study in subjects with abdominal or thoracic chronic scar pain to assess the analgesic properties of intradermal doses of Dysport®

Study Number D-FR-52120-244
Protocol Version 3.0, dated 04 December 2018

EUDRACT Number 2018-001703-37
IND Serial Number Not applicable

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AGREEMENT – SIGNATURE PAGE

Protocol Title:

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By signing below, I hereby confirm that I have read, discussed and understood the above mentioned version of the protocol and the background information concerning the study drug. I attest that I will carry out the study according to this protocol.

I also agree that the work will be performed according to Good Clinical Practice (GCP) guidelines, the ethical principles, as referenced in Section 13, and all currently applicable laws and regulations of the country(ies) where the study will be conducted.

Principal Investigator

PPD

Date 7 Dec 2018

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Sponsor

PPD

Date

Signature

PPD

SYNOPSIS

Sponsor name	Ipsen Innovation SAS
Name of finished product	Dysport®
Name of active ingredient	Clostridium botulinum toxin type A haemagglutinin complex (BTX-A-HAC)
Title of the study	A double-blind, randomised, placebo controlled, proof-of-concept study in subjects with abdominal or thoracic chronic scar pain to assess the analgesic properties of intradermal doses of Dysport®
Sponsor study number	D-FR-52120-244
EUDRACT number	2018-001703-37
IND serial number	Not applicable
Phase of development Type of study	Phase 2 Proof-of-concept
Number of planned centres	One site in the United Kingdom (UK)
Objectives	Primary • To describe the pharmacodynamic analgesic profile (time of onset of meaningful analgesic effect, peak-effect, time to peak-effect, duration of effect) of intradermal doses of Dysport in subjects with abdominal or thoracic chronic scar pain. Secondary • To compare the efficacy of intradermal doses of Dysport to placebo. • To assess the safety and tolerability of a range of intradermal doses of Dysport. Exploratory • To explore improvement of quality of life (QoL) using SF-36 questionnaire. • To explore concomitant use of rescue medication (analgesia).
Study design	The study will consist of two sequential parts, the first being to identify subjects who will potentially benefit from intradermal Dysport injection, 'responders', who will then progress to the second part, which is the double-blind study of the intradermal injection of Dysport or placebo: • Part A: A double-blind, randomised, initial two-period cross-over run-in part, extended screening period of placebo or local anesthetic (lidocaine), • Part B: A single-dose, double-blind, randomised, parallel part with one of the three different doses of Dysport or placebo. To ensure subjects will potentially benefit from intradermal injection of Dysport, they will be tested for responsiveness to local anaesthetic (lidocaine). In Part A, and upon consent and successful screening of medical eligibility, subjects will be injected (injection test 1) during a pre-randomisation run-in period in a double blind fashion with either saline or local anaesthetic (lidocaine) and assessed for pain perception up to 24 hours post-injection. One week later, they will be crossed over, injected with the other agent (injection test 2) and assessed for pain perception up to 24 hours post-injection. Pain intensity will be scored using a 11-point numerical rating scale (NRS) (from score 0 for "no pain" up to 10 for "worst possible pain"). If subjects are assessed as responders, they will enter in Part B, and will be trained and provided with an Actiwatch® to enable them to record their spontaneous NRS scores. Before dosing on Day 1, the subjects will perform baseline assessments including: • diaryassessing allodynia, hyperalgesia and conditioned pain modulation, • Completion of a QoL questionnaire,

	• Safety assessments (physical examination, vital signs measurements, collection of adverse events (AEs) and recording of concomitant medication). Subjects will be dosed if considered as consistent in pain perception from the screening visit (i.e. variability < 2 for the average spontaneous NRS score pre-injection tests in Part A, pre-QST and pre-dosing, and clinically plausible as per investigator's judgement). Subjects will then be assessed for pharmacodynamics and safety for up to 16 weeks post-dose. Subjects will be discharged from the study after safety assessments (physical examination, vital signs) during an end of study (EoS) visit.
Planned number of subjects	Approximately 24 subjects are expected to be randomised in Part B into four arms, each with six subjects treated with either one dose of Dysport or placebo. Subjects who withdraw within the first six weeks after investigational medicinal product (IMP) dosing will be replaced. Replacement subjects will receive the same schedule and treatment as the subject they have replaced. Approximately 60 subjects are expected to enter the Part A to reach the targeted randomised subject number in Part B.
Eligibility criteria	<u>Inclusion criteria</u> (1a) Male and female subjects aged between 18 and 75 years inclusive at the time of giving informed consent. (2) Subjects suffering from an area of chronic pain post-abdominal or thoracic surgery, chronic abdominal or thoracic scar pain. (3) Longitudinal axis of the pain area of 10 cm long maximum (as mapped upon screening). (4) Subjects with moderate to severe pain, i.e. spontaneous NRS score of 4-8 which has been stable for the previous month before screening. (5) Stable use of analgesics (or any medication impacting pain perception) during the month before screening and expected to be stable for the study duration. (6) Under stable medication regimen for other medication, i.e. during the month before screening. (7a) Time from surgery which caused the painful scar more than six months and less than ten years at screening. (8) No other distracting pain either chronic or acute. (9) Female subjects of childbearing potential must have a negative urine pregnancy test result and be willing to use reliable contraceptive measures throughout study participation. Reliable forms of contraception include but are not limited to hormonal contraceptives (e.g. oral, patch, injection), double-barrier (e.g. male condom plus spermicide, or female diaphragm plus spermicide), intrauterine device, male partner has had a vasectomy, total abstinence from intercourse with male partners (periodic abstinence is not acceptable). Female subjects meeting any of the following criteria are not considered to be of childbearing potential: postmenopausal (≥ 47 years of age and amenorrhoeic for at least 12 consecutive months), have been sterilised surgically (e.g. bilateral tubal ligation), have had a hysterectomy, have had a bilateral oophorectomy. (10) The subject's primary care physician has provided evidence which can be used to confirm that within the last 12 months of dosing that there is nothing in their medical history that would preclude their enrolment into a clinical study. <u>Exclusion criteria</u> (1) Previous treatment with BTX (any serotype) during the past six months before screening.

	(2) History of hypersensitivity to any of the components of the Dysport formulation (which includes human serum albumin and lactose) or allergy to cow's milk protein. (3) Known hypersensitivity to lidocaine or other anaesthetics of the amide type, known hypersensitivity to hydroxybenzoates, complete heart block, hypovolaemia. (4) Any medical condition that may put the subject at risk with exposure to BTX, including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other disease that might interfere with neuromuscular function. (5) Opioid analgesic use at a Morphine Equivalent Dosage (MED) of >75mg per day. (6) Neuroma in the scar pain area, diagnosed per ultrasound. (7) Use of agents that could interfere with neuromuscular transmission, including calcium channel blockers, penicillamine, aminoglycosides, lincosamides, polymixins, magnesium sulphate, anticholinesterases, succinylcholine and quinidine. (8) Need of any prohibited medication. (9) Any abnormal laboratory value, physical examination, vital signs, or electrocardiogram (ECG) that, in the opinion of the investigator, is clinically significant and that would compromise the safety of the subject in the study. (10) Positive for hepatitis B antigen or hepatitis C virus ribonucleic acid, positive results for human immunodeficiency virus, or who receives diagnosis for acquired immunodeficiency syndrome. (11) Positive urine screen for drugs of abuse (except for cotinine and unless explained by the investigator for therapeutic use of medication) or any history of drug or alcohol abuse, misuse, physical or psychological dependence, mood changes, sleep disturbance and functional capacity which have an impact on pain perception. (12) Significant neurological or psychiatric disorders including mental instability (unrelated to the pain) that could interfere with pain assessments; other pre-existing pain syndromes, acute or chronic, that might impair the assessment of the scar pain. (13) Any medical history of significance and/or inadequately controlled such as cardiovascular (e.g. uncontrolled high blood pressure, high risk of cardiovascular events, severe heart failure), pulmonary (e.g. uncontrolled asthma or emphysema), heamatologic, (e.g. coagulopathy/bleeding disorders), neurological (e.g. swallowing problems, blurred or double vision, trouble saying words clearly (dysarthria), hoarseness or change or loss of voice (dysphonia)), liver disease (e.g. severe hepatic impairment), kidney disease (e.g. impaired renal function in subjects taking diuretics, angiotensin converting enzyme (ACE)-inhibitors, or angiotensin II antagonists), endocrine, immunologic, dermatologic painful conditions or any other conditions that may compromise in the opinion of the investigator the ability of the subject to participate in the study. (14) If in the investigator's opinion there are any factors that may confound the analysis of the study regarding efficacy and safety (e.g. NRS > 9). (15) Previous randomisation in this study. (16) Subjects who participated in a clinical research study involving a new chemical entity or an experimental drug within 30 days before screening. (17) Subjects who are incapable of complying with the protocol in the judgment of the investigator.
Agent: Route, strength, regimen for	Lidocaine hydrochloride 0.5% v/w solution for injection in 10-mL ampoules.

the pre-randomisation run-in period (Part A)	0.5 mL (2.5 mg) of lidocaine per injection point will be injected subcutaneously (maximum 10 injection points).
Placebo agent: Route, strength, regimen for the pre-randomisation run-in period (Part A)	Sterile and preservative-free sodium chloride solution 0.9% v/w solution for injection (saline) 10-mL ampoules. 0.5 mL of saline solution per injection point will be injected subcutaneously (maximum 10 injection points).
Treatment: Route, strength, regimen for the randomised double-blind period (Part B)	Dysport will be supplied as a white lyophilised powder in a vial containing 500 U of BTX-A-HAC. 0.2 mL of 2.5, 10 or 20 U of Dysport per injection point will be injected intradermally (maximum 10 injection points, 200 U maximum).
Placebo treatment: Route, strength, regimen for the randomised double-blind period (Part B)	Placebo will be supplied as a white lyophilised powder in a vial containing the excipients from Dysport. 0.2 mL of Dysport placebo per injection point will be injected intradermally (maximum 10 injection points).
Criteria for evaluation (endpoints) for the randomised double-blind period	<u>Pharmacodynamics</u> • Time to onset, i.e. time to decrease from baseline of two points in the spontaneous NRS score, • Peak-effect, i.e. maximal decrease from baseline in the spontaneous NRS score, • Time to peak-effect, i.e. time to reach the peak-effect, • Duration of effect, i.e. duration between time to onset and last timepoint with change from baseline in the spontaneous NRS score is ≥ two points, • Change from baseline in the spontaneous NRS score to each scheduled timepoint, • Change from baseline in the stimulus-evoked NRS score to each scheduled timepoint. <u>Safety and tolerability</u> • Monitoring of treatment emergent AEs (TEAEs) and concomitant medications, • Changes from baseline in physical examination findings (including examination of the scar at the injection sites) and vital signs recordings at each scheduled timepoint. <u>Exploratory</u> • Change from baseline in SF-36 scores at each scheduled timepoint, • Amount of rescue medication taken during the study, • Time to first intake of rescue medication.
Statistical methodology	This is an exploratory study to assess how Dysport might be of benefit in chronic pain. An appropriate sample size cannot be determined statistically as insufficient human data are available from previous clinical trials. Approximately 24 subjects (six subjects per treatment arm) will be randomised in the double-blind period (Part B). Subjects who withdraw within the first six weeks after IMP dosing for reasons other than lack of efficacy will be replaced. Only descriptive statistics will be provided.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

RATIONALE FOR PROTOCOL AMENDMENT # 2

The overall changes and rationale for the changes made to this protocol are as follows:

- A maximum age of the subject for inclusion to the study was increased to 75 years old. The following inclusion criterion is updated accordingly *'Male and female subjects aged between 18 and 75 years inclusive at the time of giving informed consent*'. Raising the upper age limit of subjects to 75 years would enhance the value of the study, given the frequency of surgery in the older age group, particularly the frequency of post-surgical neuralgia after incisional cancer surgery for chest and abdominal tumours.

  The sponsor has an extensive experience with Dysport for different indications, for more than 25 years postmarketing experience, with continuous monitoring of safety data via signal detection activities in approved indications: both aesthetic and spasticity and other therapeutic indications with various routes of administration, including intramuscular, subcutaneous, and intradermal. The safety profile due to the route of administration is not different in terms of localised reactions between various age groups. The current labelling for Dysport contains the following recommendations for treating physicians for elderly patients (≥ 65 years): Clinical experience with Dysport has not identified differences in response between the elderly and younger adult patients. In general, elderly patients should be observed to evaluate their tolerability of Dysport, due to the greater frequency of concomitant disease and other drug therapy. Considering the well-established safety profile of Dysport and the Sponsor's assessment of the proposed changes, the overall risk benefit of the study remains favourable.

- The time from surgery which caused the painful scar for inclusion to the study was extended to ten years. '*Time from surgery which caused the painful scar more than six months and less than ten years at screening'*.
  Extension of the duration from five to ten years is considered acceptable providing the pain is clearly associated with previous abdominal or thoracic surgery, and the subject can consistently define and rate the pain area in an objective and plausible manner. It is now held that painful conditions with clear aetiology related to diagnosed tissue damage/disease remain reversible with effective treatment. This is distinct from cases where there may be significant psycho-social factors (e.g. acquired mental health issues; ongoing litigation, severe 'illness behaviour' etc), widespread bodily pain. The pain associated with the wound or scar is classically in a small well defined area, with the subject able to consistently reproduce the mapped area. Indeed this is a requirement for screening and subsequent visits. It is our contention that the reliability of these criteria is crucial, while the duration of such pain is at most a minor factor.

- Two parts of the QST test (punctate hyperalgesia, vibration disappearance) won't be performed for the following reasons:
  1. Punctate hyperalgesia – This test uses a painful stimulus (Neurotips) which has to be applied to an already painful area. As this test would not be repeated at Week 6 and Week 12 after treatment, we consider not to perform it at baseline in subjects already experiencing moderate to severe pain at the level of their scar.
  2. Vibration disappearance - This test using a tuning fork requests a bony prominence closest to the test site. In the context of this study where location of the painful area might vary (abdominal, thoracic scar), the corresponding bony prominence might differ from one subject to another and introduce variability in the conduct of the

procedure. As this test would not be repeated at Week 6 and Week 12 after treatment, Sponsor considers not to perform it at baseline.

QST at baseline will thus consists of the same series of tests (i.e. using light touch, pressure and temperature stimuli only) as those to be conducted at Week 6 and Week 12. This series of tests will consist of:

- Baseline assessments (NRS score)
- Sensory threshold
- Pain perception threshold
- Static mechanical allodynia
- Dynamic mechanical allodynia
- Temporal summation
- Pressure pain threshold
- Conditioned pain modulation
- Temperature threshold

All modifications are presented in the Attachment 6.

PROTOCOL HISTORY

Protocol version	Rationale for amendment
V1.0, 25-MAY-2018	Not applicable, initial version
V2.0, 13-AUGUST-2018 Amendment #1	• Upon request of the Ethics Committee, and to ensure patient beneficence, the following statement is added to section 5.2.4 'The principal investigator will inform the family doctor and pain clinic (if applicable) with details of participation in the clinical study and any relevant information which may help the treating physician in the management of their patient'. • Upon request of the Ethics Committee, and to clarify how participants would be monitored through each stage of the study, the following statement is added to section 5.1 'Subjects will be monitored throughout the study with review of their pain scores at both telephone and physical visits to site. In addition, the subjects can contact the site at any time and if required an unscheduled visit can be performed to assess the subject and their participation in the study'. • As advised by the Medicines and Healthcare products Regulatory Agency (MHRA), the following criterion 'The subject's primary care physician has provided evidence which can be used to confirm that within the last 12 months of dosing that there is nothing in their medical history that would preclude their enrolment into a clinical study' is added to the list of inclusion criteria and removed from the list of exclusion ones. • The following inclusion criterion 'Under stable medication regimen for other medication, i.e. during the

	month before screening' was listed in section 4.1 of the protocol, but was missing in the synopsis. The list of inclusion criteria in the synopsis is updated accordingly. • A maximum opioid dosage use is defined for inclusion to the study. The following exclusion criterion is added accordingly 'Opioid analgesic use at a Morphine Equivalent Dosage (MED) of >75 mg per day'. • The list of medications that should not start during the study is also updated. 'High doses of opioids i.e. equivalent to morphine (oral) 100 mg/day, or equivalent as defined in the British national formulary ' is replaced by 'Opioids'.
V3.0, 04-DECEMBER-2018 Amendment #2	See rationale for protocol amendment #2 (above)

LIST OF DEFINITIONS AND ABBREVIATIONS

DEFINITIONS	Wording Definition
Audit	Systematic and independent examination of the study-related activities and documents to determine whether the evaluated study-related activities were conducted, and the data were recorded, analysed, and accurately reported according to the protocol, sponsor's standard operating procedures, good clinical practices, and the applicable regulatory requirement(s).
Compliance	Adherence to all the study-related requirements, good clinical practices requirements and the applicable regulatory requirements.
Double-blinding	Procedure to which usually the subject(s), investigator(s), monitor(s), and in some cases, selected sponsor personnel, are being unaware of the treatment assignment(s).
End of Study	Date of the last visit or last scheduled procedure shown in the study schedule for the last active subject in the study.
Enrol / Randomise	Act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
Enter / Consent	Act of obtaining informed consent for participation in a clinical study from subjects deemed- or potentially eligible to participate in the clinical study. Subjects entered into a study are those who sign the informed consent document directly.
Ethics Committee	Board or committee (institutional, regional, or national) composed of medical professional and non-medical members whose responsibility is to verify that the safety, welfare, and human rights of the subjects participating in a clinical study are protected.
Investigator	Physician responsible for the conduct of a clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
Run-in	Extension of the screening period to select subjects who have potential to respond to Dysport.
Screen	Act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves invasive procedures (for example, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained.
Subject	Individual who is or becomes a participant in clinical research, either as a recipient of the test article or as a control.

ABBREVIATION	Wording Definition
ACE	Angiotensin converting enzyme
AE	Adverse event
AESI	Adverse event of special interest

DEFINITIONS	Wording Definition
BTX	Botulinum neurotoxin
BTX-A	Botulinum neurotoxin serotype A
BTX-A-HAC	Botulinum neurotoxin type A haemagglutinin complex
CA	Competent Authority
CFR	Code of Federal Regulations (United States of America)
CGRP	Calcitonin gene-related protein
CRO	Contract research organisation
CRU	Clinical research unit
DBP	Diastolic blood pressure
DOA	Drug of abuse
DRG	Dorsal root ganglion
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ED	Early discontinuation
EoS	End of study
FDA	Food and Drug Administration
GCP	Good clinical practice
GPS	Global patient safety
HR	Heart rate
IB	Investigator's brochure
ICH	International Council for Harmonisation
IEC	Independent Ethic Committee
IMP	Investigational medicinal product
IND	Investigational new drug
IRB	Independent Review Board
MED	Morphine equivalent dosage
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NRS	Numerical rating scale
PP	Per protocol
PPT	Pressure pain threshold
QoL	Quality of life

DEFINITIONS	Wording Definition
QST	Quantitative sensory testing
SAE	Serious adverse events
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SmPC	Summary of product characteristics
SNAP-25	Synaptosomal-associated protein 25
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent adverse event
TFLs	Tables, figures, and listings
TMF	Trial master file
TRPV1	Transient receptor potential vanilloid 1
UK	United Kingdom
WHO	World Health Organisation

1 BACKGROUND INFORMATION

1.1 Introduction

Pain is the most common symptom for which subjects seek medical attention, but pain management has unmet needs. Pain is the most frequent reason why subjects visit an emergency department and there is a need for additional research on the relative safety and efficacy of non-opioid approaches to emergency department analgesia (Todd, 2017). Chronic pain affects between one-third and one-half of the population of the United Kingdom (UK), corresponding to just under 28 million adults and is likely to increase due to an ageing population (Fayaz et al., 2016).

Pain is defined by the International Association for the Study of Pain as: "*An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage*" (www.iasp-pain.org). Pain is subjective and this definition links emotion and past experience to the sensory event thus also highlighting that pain is a complex experience that includes multiple dimensions. This is because each individual learns the meaning of the word "pain" through experiences related to injury in early life. Stimuli or illnesses that cause pain are likely to damage tissue and hence pain is an experience associated with actual or potential tissue damage. Pain is almost always unpleasant and therefore an emotional experience. Pain is subjective and there are no satisfactory objective measures of pain, hence the subject's self report of pain is the most reliable indicator of pain (American Pain Society, 2006).

Clostridial neurotoxins from the botulinum neurotoxin (BTX) family are protein complexes, derived from the bacterium *Clostridium botulinum*, which potently inhibit acetylcholine release and results in a reversible blockade of the neuromuscular junction. This feature led to the clinical development of BTX for neuromuscular disorders. Serotype A BTX (BTX-A) are commercially available and clinically used for treatment of disorders characterised by increased tonicity or overactivity of specific muscles (Barnes, 2003; Thenganatt et al., 2012), and also for treatment of overactivity of secretory glands (Heckman et al., 2001). Along with the neuroparalytic effect, it has been reported that BTX-A reduces the pain associated with the neuromuscular hyperactivity disorders, such as torticollis (Tsui et al., 1985; Brin et al., 1987; Tarsy, 1999).

BTX-mediated pain relief was initially described in conditions associated with muscle contraction and believed to be associated with decreased contraction of affected muscles (Arezzo, 2002; Cohen et al., 1989; Mense, 2004). It was proposed that BTX-A, by inhibiting the release of acetylcholine in hyper-functional muscular end plates, may indirectly prevent the painful ischaemia caused by muscle contractures in spasticity and dystonia (Mense, 2004). However, it was reported that the observed pain relief in patients treated for spasmodic torticollis was not concurrent with neuromuscular effects since it was present in some patients even when dystonic posture of the neck was not improved (Stell et al., 1988). Additionally, BTX-A-mediated pain relief does not always occur simultaneously with the observed paralytic effect in focal dystonias, and it sometimes even persists after the neuromuscular benefit is no longer visible (Aoki, 2003; Freund, 2003). Since the onset of BTX-A action on pain did not correspond to the onset of paralytic muscular effects or lasted longer than the paralysis, toxin action on sensory or vegetative nerves was suggested (Giladi, 1997; Mense, 2004).

Independently from pain which might be related to increased muscle contraction, the anti-nociceptive effect of BTX-A was also reported in different types of chronic pain not associated primarily with muscle hyperactivity, such as migraine (Silberstein et al., 2000; Luvisetto et al., 2015) and different types of neuropathic pain (Argoff, 2002; Attal et al., 2016).

Along with experimental knowledge obtained from preclinical studies, it is now accepted that BTX-A effects on pain may be mediated by its direct effects on sensory nerves, and current

evidence suggests several possible peripheral nervous system and central nervous system mechanisms of action, which might account for the analgesic action of peripherally administered BTX-A across the whole nociceptive pathway (Pellett et al., 2015):

- BTX-A acts on neurons involved in pain perception and prevents the release of other neurotransmitters than acetylcholine, e.g. glutamate, substance P, calcitonin gene-related protein (CGRP) and vasopressin as demonstrated in vitro from cultured cells or isolated materials (Mc Mahon et al., 1992; Purkiss et al., 2000) and also in vivo in preclinical pain models, e.g. in the rat formalin test (Cui, 2004) or the rat capsaicin pain model (Bach-Rojecky, 2005; Filipovic et al., 2012; Marino et al., 2014),
- BTX-A may regulate the expression of a variety of receptors and channels implicated in peripheral sensitisation, amongst which vanilloid receptors such as the transient receptor potential vanilloid 1 (TRPV1) (Apostolidis et al., 2005) whose mobilisation from intracellular stores to the plasma membrane involves regulated exocytosis (Dolly et al., 2009) and cleavage of the synaptosomal-associated protein 25 (SNAP-25) (de Paiva et al., 1993),
- Following endocytosis in the peripheral terminals, some molecules of BTX-A may undergo retrograde transport along the axon and reach the dorsal root ganglion (DRG) neurons where they would block the vesicular release of neurotransmitters into the extracellular milieu of the DRG, which would otherwise activate and excite the neighbouring sensory neurons (Dickenson, 1987a; Matak et al., 2012),
- Though speculative, BTX-A may also further undergo intra-vesicular trafficking to the central terminals, and block neurotransmission into the brainstem and higher centres for pain integration (Coderre et al., 1990; Dickenson, 1987b).

Dysport® is the trade name for an injectable form of BTX-A, which is isolated and purified from the bacterium *Clostridium botulinum*. Dysport was first registered for the treatment of blepharospasm and hemifacial spasm in the UK in 1990. It is licensed in more than 85 countries for various indications including: spastic equinus foot deformity due to spasticity in adults following a stroke, blepharospasm, adult upper and lower limb spasticity, hemifacial spasm, spasmodic torticollis (also known as cervical dystonia), paediatric lower limb spasticity and dynamic equinus foot deformity due to cerebral palsy, axillary hyperhidrosis, and glabellar lines.

The present study will investigate the analgesic effects of different doses of Dysport in subjects experiencing chronic pain from an abdominal or thoracic scar (chronic post-surgical pain; post-surgical neuralgia).

1.2 Name and Description of the Investigational Medicinal Product

Dysport is formulated as a complex of BTX-A with haemagglutinin (BTX-A-HAC), a large therapeutically inert protein used to stabilise the toxin. Dysport is formulated with lactose (bulking agent) and human serum albumin, and is supplied as a lyophilised powder.

A detailed description can be found in the Summary of Product Characteristics (SmPC).

1.3 Non-Clinical Data

The analgesic properties of commercially available BTX-A have been investigated in a variety of acute and chronic animal pain models. The effectiveness of BTX-A has specifically been demonstrated in formalin- (Cui, 2004; Luvisetto et al., 2006) and capsaicin-induced pain models (Marino et al., 2014; Ramachandran et al., 2015), as well as in arthritic rats (Krug et al., 2009) and dogs (Heikkila et al., 2014). Positive outcome following

administration of BTX-A has also been evidenced in mononeuropathy (peripheral and infraorbital nerve ligation, ventral root transection), polyneuropathy (chemotherapy-induced, diabetes) and trigeminal murine pain models (Favre-Guilmard et al., 2009; Bach-Rojecky et al., 2010; Gazerani et al., 2010; Filipovic et al., 2012; Shimizu et al., 2012; Park et al., 2015).

1.4 Clinical Data

Botulinum toxin injection is being increasingly used "off-label" in the clinical management of chronic pain, and there have been a number of reviews highlighting the role of treating painful conditions with BTX. In their review of BTX in the treatment of chronic pain, Rivera Dia et al. (2014) discuss several conditions where BTX may have a role, such as trigeminal neuralgia, tension headache, chronic migraine, myofascial pain, phantom limb pain and joint pain. Park and Park (2017) also reviewed the experimental and clinical evidence of the mechanism by which BTX acts on various types of neuropathic pain. They described how BTX can be applied as treatment for neuropathic pain conditions such as postherpetic neuralgia, post-surgical neuralgia, diabetic neuropathy, occipital neuralgia or spinal cord injury induced neuropathic pain. They also provide clear evidence that BTX has an analgesic effect involving both peripheral and central elements of the nociceptive pathway for chronic neuropathic and nociceptive pain.

Besides use for aesthetic treatments and infocal hyperhidrosis, BTX has also been recently used experimentally in many other dermatological conditions with good results. Campanati et al. (2017) analysed the possible BTX "off-label" applications in dermatology and specifically collected published data on the application of BTX-A injections in keloids and hypertrophic scars. The studies reviewed revealed a great potential for BTX-A with improvement of the lesions such as lowering of the erythema, decrease of the itching, pain and tenderness sensation, but also decrease in size and flattening of the lesions. Overall, the therapeutic satisfaction of the patient and physician was good in the studies reviewed.

Of relevance for the present study, Schwartz et al. (2004) investigated the effects of intradermal injections of BTX-A in relieving chronic post-surgical scar pain. They showed that subjects treated with BTX-A exhibited an improved reduction in mean pain scores relative to dexamethasone (30% versus 25%) and twice the duration of effect (eight weeks for BTX-A versus four weeks for dexamethasone).

1.5 Rationale for the Study

The rationale of this study is to test the hypothesis that Dysport is effective in relieving chronic scar pain when administered intradermally. This study will also aim at characterising the pharmacodynamic profile of any analgesic effect of a predefined dose range (time to onset, peak-effect, time to peak-effect and duration of effect).

1.6 Dosage Selection

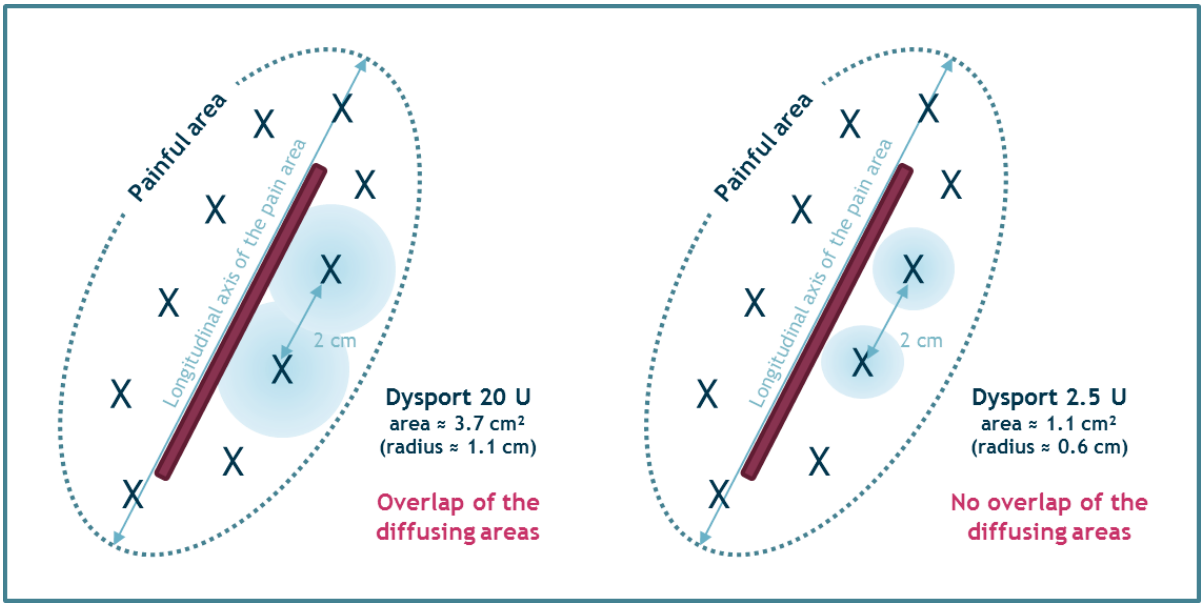
The anhidrotic properties of a range of single intradermal 0.2 mL doses of Dysport (2.5, 10 and 20 U) were studied in healthy volunteers (Ipsen Study CCI [redacted]). These doses were well tolerated and showed a dose-related increase in the anhidrotic area using the Minor's starch-iodine test. The maximal mean areas were 1.1, 2.7 and 3.7 cm² (corresponding radius of 0.6, 0.9 and 1.1 cm) for 2.5, 10 and 20 U respectively.

Those same dose levels of 2.5, 10 and 20 U and route of administration have been selected for the individual injection points in the present study.

The minimal dose will be 2.5 U injected in four sites (i.e. total dose of 10 U).

The maximal diffusion radius (1.1 cm for Dysport 20 U), together with the specification related to the maximal length of the pain area (i.e. no more than 10 cm) have been taken into consideration for the injection paradigm where individual injection points will be given intradermally 2 cm apart and the maximal number of injection points limited to 10 (see Figure 1). The maximal allowed total dose in the present study will thus be 200 U in the Dysport maximal dose group (20 U), which is consistent with the maximal recommended intradermal dose in the product label.

Figure 1 Injection Paradigm



1.7 Population to be Studied

This study will enrol male and female subjects with a painful abdominal or thoracic scar. Pain should be rated as moderate to severe i.e. numerical rating scale (NRS) score between 4 and 8 on an 11-point scale (0-10), and stable within one month before screening. The pain should also be chronic, i.e. persistent for more than six months after the surgery which led to the painful scar.

To ensure subjects will potentially benefit from intradermal injection of Dysport, they will be tested for responsiveness to local anaesthetic (lidocaine) during a pre-randomisation run-in period. This is consistent with use of diagnostic local anaesthetic blocks which are used to obtain information about of the source of subject's pain, being target specific and controlled in order to exclude false positive results (Bogduk, 2002). This assessment will be performed by investigators with experience in managing subjects with painful conditions and pain studies.

1.8 Known and Potential Risks to Human Subjects

Dysport is licensed in the UK for the symptomatic treatment of focal spasticity, spasmodic torticollis, blepharospasm and hemifacial spasm, injected either intramuscularly or subcutaneously targeting the affected muscles or muscle groups, and is also licensed for treatment of severe primary hyperhidrosis of the axillae, injected intradermally.

Side effects of Dysport as experienced with intradermal injection for hyperhidrosis indication were local injection site reactions including pain, bruising, pruritis, and oedema. In addition, rash and compensatory sweating were also reported.

The maximum licensed intradermal dose is 200 U per area of injections. This maximum recommended intradermal dose will not be exceeded in the present study. Additional information regarding risks to human subjects may be found in the SmPC.

Overall, the safety profile of Dysport is well established after more than 20 years of clinical trials and post-marketing experience in various therapeutic and aesthetic indications at various doses with maximum dose used for intradermal indication up to 200 U at single area of injections. In the current proposed study in subjects with chronic scar pain, we believe the risk associated with Dysport use intradermally, to be acceptable, considering the established and known safety profile with intradermal use.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To describe the pharmacodynamic analgesic profile (time of onset of meaningful analgesic effect, peak-effect, time to peak-effect, duration of effect) of intradermal doses of Dysport in subjects with abdominal or thoracic chronic scar pain.

2.2 Secondary Objectives

- To compare the efficacy of intradermal doses of Dysport to placebo.
- To assess the safety and tolerability of a range of intradermal doses of Dysport.

2.3 Exploratory Objectives

- To explore improvement of quality of life (QoL) using SF-36 questionnaire.
- To explore concomitant use of rescue medication (analgesia).

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

The study will consist of two sequential parts, the first being to identify subjects who will potentially benefit from intradermal Dysport injection, 'responders', who will then progress to the second part, which is the double-blind study of the intradermal injection of Dysport or placebo:

- Part A: A double-blind, randomised, initial two-period cross-over run-in part, extended screening period of placebo or local anaesthetic (lidocaine),
- Part B: A single-dose, double-blind, randomised, parallel part with one of the three different doses of Dysport or placebo.

To ensure subjects will potentially benefit from intradermal injection of Dysport, they will be tested for responsiveness to local anaesthetic (lidocaine).

In Part A, and upon consent and successful screening of medical eligibility, subjects will be injected (injection test 1) during a pre-randomisation run-in period in a double blind fashion with either saline or local anaesthetic (lidocaine) and assessed for pain perception up to 24 hours post-injection. One week later, they will be crossed over, injected with the other agent (injection test 2) and assessed for pain perception up to 24 hours post-injection. Pain intensity will be scored using a 11-point NRS (from score 0 for "no pain" up to 10 for "worst possible pain").

If subjects are assessed as responders, they will enter in Part B, and will be trained and provided with an Actiwatch® to enable them to record twice a day their spontaneous NRS scores.

Before dosing on Day 1, the subjects will perform baseline assessments including a quantitative sensory testing (QST) assessing allodynia, hyperalgesia and conditioned pain modulation, completion of a QoL questionnaire, and safety assessments (physical examination, vital signs measurements, collection of adverse events (AEs) and recording of concomitant medication).

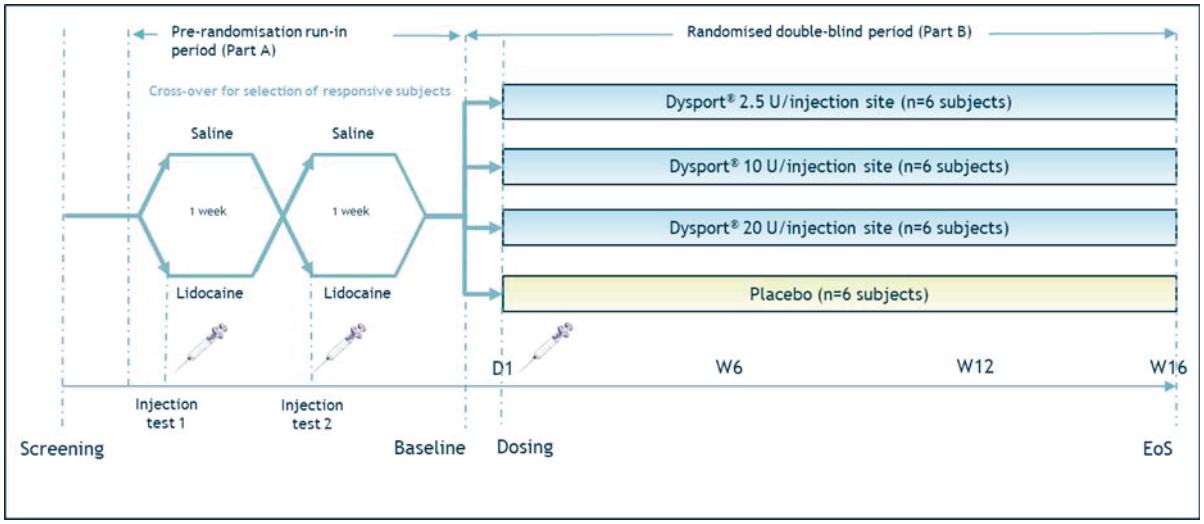
Subjects will be dosed if considered as consistent in pain perception from the screening visit (i.e. variability < 2 for the average spontaneous NRS score pre-injection tests in Part A, pre-QST and pre-dosing and as clinically plausible per investigator's judgement).

Subjects will then be assessed for pharmacodynamics and safety for a total of 16 weeks post-dose.

Subjects will be discharged from the study after safety assessments (physical examination, vital signs) during an end of study (EoS) visit.

The study design is presented in Figure 2.

Figure 2 Study Design



3.2 Study Endpoints

3.2.1 Primary Endpoints

The primary endpoints will be:

- Time to onset, i.e. time to decrease from baseline of two points in the spontaneous NRS score,
- Peak-effect, i.e. maximal decrease from baseline in the spontaneous NRS score,
- Time to peak-effect, i.e. time to reach the peak-effect,
- Duration of effect, i.e. duration between time to onset and last timepoint for which change from baseline in the spontaneous NRS score is ≥ two points.

3.2.2 Secondary Endpoints

The following secondary endpoints will be evaluated:

- Change from baseline in the spontaneous NRS score to each scheduled timepoint,
- Change from baseline in the stimulus-evoked NRS score to each scheduled timepoint,
- Safety of three intradermal doses of Dysport. Safety assessments will include monitoring of AEs, concomitant medications and changes from baseline in physical examinations findings including the examination of the scar at the injection sites and vital signs recordings at each scheduled timepoint.

3.2.3 Exploratory Endpoints

The following exploratory endpoints will be evaluated:

- Change from baseline in SF-36 scores at each scheduled timepoint,
- Amount of rescue medication taken during the study,
- Time to first intake of rescue medication.

3.3 Study Duration

This study will consist of:

- A screening visit: 28 days maximum before IMP dosing,
- A Part A, pre-randomisation run-in period:
  - First injection test: 21 days maximum before IMP dosing,

- Second injection test: one week after first injection test, 14 days maximum before IMP dosing,

- A Part B, randomised double-blind period:
  - A baseline period including a QST and Actiwatch® training, safety assessments and a QoL: within 7 days before IMP dosing,
  - A one-day IMP dosing,
  - A 16-week randomised double-blind period.

Subjects are expected to participate in this study for a maximum of 20 weeks.

The study will be considered to have started when the first subject has provided signed informed consent and will be considered to have ended after the last subject has completed his EoS visit.

The overall study is anticipated to last approximately one year.

3.4 Randomisation and Blinding

3.4.1 Method of Randomisation

At screening, potential subjects will be allocated an 11-digit subject number consisting of:

- The country code (three digits),
- The centre number (three digits),
- The sequential order of entry of the subject in the unit (five digits).

3.4.1.1 Pre-randomisation Run-in Period (Part A)

Following confirmation of eligibility after the screening visit, subjects will be assigned to a pre-randomisation run-in number and allocated to one of the two treatment sequence groups in a chronological order, i.e. first eligible subject after the screening visit will be given the first run-in number (as detailed in Table 1). Subjects will be randomised with a ratio 2:2 (blocks of eight subjects) to receive:

- Either lidocaine on injection test 1 then placebo (saline) on injection test 2,
- Or placebo (saline) on injection test 1 then lidocaine on injection test 2.

Table 1 Part A Pre-randomisation Run-in Numbers

Part A Pre-randomisation Run-in Numbers
From CCI

3.4.1.2 Randomised Double-blind Period (Part B)

Subjects will be randomised to receive Dysport 2.5 U, Dysport 2.5 U placebo, Dysport 10 U, Dysport 10 U placebo, Dysport 20 U, Dysport 20 U placebo with a ratio 3:1:3:1:3:1 (blocks of 12 subjects).

Following confirmation of eligibility after injection test 2, subjects will be assigned to a randomisation number and allocated to one of the treatment groups in a chronological order, i.e. first eligible subject will be given the first randomisation number as detailed in Table 2.

Table 2 Part B Randomisation Numbers

Part B Randomisation Numbers	Part B Replacement Randomisation Numbers
From CCI	From CCI

Mirror lists of randomisation numbers will also be produced to allow the randomisation of replacement subjects (e.g. the subjects who withdraw within six first weeks after IMP dosing) or to be used for the replacement of kits which could be damaged during the IMP reconstitution. For example, number CCI will be used to randomise the replacement for the subject who was randomised with number CCI.

The sponsor's randomisation manager will prepare and keep the master lists of pre-randomisation run-in numbers and randomisation numbers. A copy of these lists will be sent confidentially to:

- Pharmaceutical Development Clinical Supply Chain
  Beaufour Ipsen Industrie SAS
  Rue d'Ethe Virton
  28100 Dreux, France.

The lists and their copies will be kept confidential in secure locations. Access to the randomisation lists will be restricted until authorisation is given to release them for final analysis.

An identification code assigned to each subject will be used in lieu of the subject's name to protect the subject's identity when reporting AEs and/or other study-related data.

3.4.2 Blinding

Only the pharmacist or delegate in charge of drug preparation at the clinical research unit (CRU) and the monitor responsible for pharmacy monitoring will be partially unblinded. These personnel will be fully trained on the importance of their role in maintaining the blind for the subject, the investigator and the remainder of the study team. The unblinded staff at the CRU will not carry out any study assessments other than those they are assigned to.

All other staff at the CRU, the sponsor and the subjects will be blinded to treatment allocations during the study.

3.4.3 Code-break

Two types of code-break envelopes will be set up for the pre-randomisation run-in period (Part A) and for the randomised double-blind period (Part B).

Two sets of individual sealed code-break envelopes of each type will be prepared by the sponsor's randomisation manager to enable emergency code-break procedures for individual subjects without compromising the blind of the study. One set will be provided to the CRU and one set provided to the sponsor department of global patient safety (GPS).

In an emergency situation, which requires the identification of the study treatment group, the investigator may break the treatment code. If so, the investigator is requested to:

- Inform the monitoring office at the earliest opportunity that the blind has been broken for an emergency situation,
- Reseal the code-break envelope,
- Sign, date and provide reason for the code-break on the emergency code-break form, and on the sealed envelope.

The date and reason for code-breaking should also be recorded in the electronic case report form (eCRF).

Specific case, to check if the subject is a responder at the end of the run-in period, the investigator will unblind the subject by (re-)opening the code-break-envelope associated to his(her) assigned pre-randomisation run-in number. The investigator will sign, date and specify ”End of run-in period” as the reason for the code-break on the envelope.

Monitors should routinely check the integrity of the envelopes that are stored at the study site. They must collect envelopes from the study site prior to study close-out and ensure that they are all intact. If envelope(s) have been opened at the site or by the sponsor’s representative, the monitor must ensure a written explanation is clearly documented (opener’s name, dated signature and reason for opening) on the visit status page of the eCRF.

Confirmation of the integrity of all code-break envelopes at study completion must be documented in the trial master file (TMF). All sets of the sealed individual subject envelopes must be kept in the TMF in the co-ordinating office at study completion for proof of integrity.

3.5 Stopping Rules and Discontinuation Criteria

The complete study can be terminated prematurely at any time if the sponsor judges it necessary for any reason. In that case, all scheduled procedures and assessment for subjects who are still in the study will be performed.

Some possible reasons for the closure of a study site may include:

- Failure of the investigator staff to comply with the protocol or with the GCP guidelines,
- New and significant safety concerns,
- Inadequate subject’s recruitment.

During the conduct of the study, all AEs including serious AEs (SAEs) will be reviewed as they are reported from the study site to identify new and significant safety concerns.

3.6 Source Data Recorded on the Case Report Form

Data will be collected in the eCRF in compliance with Food and Drug Administration (FDA) 21 CFR Part 11. As required by GCP, the sponsor assigned monitor will verify, by direct reference to the source documents, that the data required by the protocol are accurately reported on the eCRF. The source documents must, as a minimum, contain a statement that the subject is included in a clinical study, the date that informed consent was obtained prior to participation in the study, the identity of the study, diagnosis and eligibility criteria, visit dates (with subject status), agent and IMP administration, and any AEs and associated concomitant medications.

Definitions for source data and source documents are given below:

- Source data: All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
- Source documents: Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files, and records kept at the pharmacy, at the laboratories and at medicotechnical departments involved in the clinical study).

No source data will be directly recorded on the eCRF during the present study.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Subjects must fulfil all of the following criteria to be considered eligible for enrolment in the study.

(1a) Male and female subjects aged between 18 and 75 years inclusive at the time of giving informed consent.

(2) Subjects suffering from an area of chronic pain post-abdominal or thoracic surgery, chronic abdominal or thoracic scar pain.

(3) Longitudinal axis of the pain area of 10 cm long maximum (as mapped upon screening).

(4) Subjects with moderate to severe pain, i.e. spontaneous NRS score of 4-8 which has been stable for the previous month before screening.

(5) Stable use of analgesics (or any medication impacting pain perception) during the month before screening and expected to be stable for the study duration.

(6) Under stable medication regimen for other medication, i.e. during the month before screening.

(7a) Time from surgery which caused the painful scar more than six months and less than ten years at screening.

(8) No other distracting pain either chronic or acute.

(9) Female subjects of childbearing potential must have a negative urine pregnancy test result and be willing to use reliable contraceptive measures throughout study participation. Reliable forms of contraception include but are not limited to hormonal contraceptives (e.g. oral, patch, injection), double-barrier (e.g. male condom plus spermicide, or female diaphragm plus spermicide), intrauterine device, male partner has had a vasectomy, total abstinence from intercourse with male partners (periodic abstinence is not acceptable). Female subjects meeting any of the following criteria are not considered to be of childbearing potential: postmenopausal (≥ 47 years of age and amenorrhoeic for at least 12 consecutive months), have been sterilised surgically (e.g. bilateral tubal ligation), have had a hysterectomy, have had a bilateral oophorectomy.

(10) The subject's primary care physician has provided evidence which can be used to confirm that within the last 12 months of dosing that there is nothing in their medical history that would preclude their enrolment into a clinical study.

4.2 Exclusion Criteria

Subjects who meet any of the following criteria will not be considered eligible for enrolment in the study.

(1) Previous treatment with BTX (any serotype) during the past six months before screening.

(2) History of hypersensitivity to any of the components of the Dysport formulation (which includes human serum albumin and lactose) or allergy to cow's milk protein.

(3) Known hypersensitivity to lidocaine or other anaesthetics of the amide type, known hypersensitivity to hydroxybenzoates, complete heart block, hypovolaemia.

(4) Any medical condition that may put the subject at risk with exposure to BTX, including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other disease that might interfere with neuromuscular function.

(5) Opioid analgesic use at a Morphine Equivalent Dosage (MED) of >75mg per day.

(6) Neuroma in the scar pain area, diagnosed per ultrasound.

(7) Use of agents that could interfere with neuromuscular transmission, including calcium channel blockers, penicillamine, aminoglycosides, lincosamides, polymixins, magnesium sulphate, anticholinesterases, succinylcholine and quinidine.

(8) Need of any prohibited medication.

(9) Any abnormal laboratory value, physical examination, vital signs, or electrocardiogram (ECG) that, in the opinion of the investigator, is clinically significant and that would compromise the safety of the subject in the study.

(10) Positive for hepatitis B antigen or hepatitis C virus ribonucleic acid, positive results for human immunodeficiency virus, or who receives diagnosis for acquired immunodeficiency syndrome.

(11) Positive urine screen for drugs of abuse (except for cotinine and unless explained by the investigator for therapeutic use of medication) or any history of drug or alcohol abuse, misuse, physical or psychological dependence, mood changes, sleep disturbance and functional capacity which have an impact on pain perception.

(12) Significant neurological or psychiatric disorders including mental instability (unrelated to the pain) that could interfere with pain assessments; other pre-existing pain syndromes, acute or chronic, that might impair the assessment of the scar pain.

(13) Any medical history of significance and/or inadequately controlled such as cardiovascular (e.g. uncontrolled high blood pressure, high risk of cardiovascular events, severe heart failure), pulmonary (e.g. uncontrolled asthma or emphysema), heamatologic, (e.g. coagulopathy/bleeding disorders), neurological (e.g. swallowing problems, blurred or double vision, trouble saying words clearly (dysarthria), hoarseness or change or loss of voice (dysphonia)), liver disease (e.g. severe hepatic impairment), kidney disease (e.g. impaired renal function in subjects taking diuretics, angiotensin converting enzyme (ACE)-inhibitors, or angiotensin II antagonists), endocrine, immunologic, dermatologic painful conditions or any other conditions that may compromise in the opinion of the investigator the ability of the subject to participate in the study.

(14) If in the investigator's opinion there are any factors that may confound the analysis of the study regarding efficacy and safety (e.g. an NRS > 9).

(15) Previous randomisation in this study.

(16) Subjects who participated in a clinical research study involving a new chemical entity or an experimental drug within 30 days before screening.

(17) Subjects who are incapable of complying with the protocol in the judgment of the investigator.

4.3 Rationale for Specific Inclusion / Exclusion Criteria

Mapping of the painful area is to detect the anatomical relationship to the scar and the previous surgery, and to ensure that the longitudinal axis of the pain area length will be consistent with the injection paradigm. Pain area should be large enough to have a minimum of 4 injections and a maximum of 10 injections. This maximum of 10 injections is set so as not to exceed the maximum permitted dose (200 U of Dysport) with the highest dose (20 U). This in turn limits the maximum length of the painful area to 10 cm, with five injections, 2 cm apart, either side of the longitudinal axis of the pain area, and an estimate of approximately 1 cm spread of dose around each injection point.

4.4 Withdrawal of Subjects

In accordance with the declaration of Helsinki and International Council for Harmonisation (ICH) GCP, each subject is free to withdraw from the study at any time, for any reason (e.g. withdrawal of consent, AE).

The investigator can withdraw a subject from the study at any time for any reason (e.g. protocol deviation, non compliance with the protocol conditions, lack of cooperation, in the event of concurrent illness, AE, or other reasons concerning the health or well-being of the subject).

The reason for and date of withdrawal from the study must be recorded in the eCRF.

If withdrawal is based on subject's decision every attempt will be made to determine:

- The reason for withdrawal,
- Whether the subject also decides to withdraw his/her consent for the sponsor to collect and use the data collected up to the withdrawal point.

Data collected prior to subject withdrawal may be kept in study records and shared for further analyses unless the subject formally specifies his/her decision to withdraw consent for using data already collected.

Should a subject be withdrawn from the study after IMP dosing and before normal study completion, all efforts will be made to complete the EoS assessments and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal should be made whenever possible.

Subjects who withdraw within the first six weeks after IMP dosing for reasons other than lack of efficacy will be replaced. Replacement subjects will receive the same schedule and treatment as the subject they have replaced.

5 STUDY CONDUCT

5.1 Study Schedule of Assessments

The schedule of procedures and assessments during the study is summarised and presented in Section 18.1. Subjects will be monitored throughout the study with review of their pain scores at both telephone and physical visits to site. In addition, the subjects can contact the site at any time and if required an unscheduled visit can be performed to assess the subject and their participation in the study.

The total volume of blood drawn for each subject and all evaluations throughout this study is detailed and presented in Section 18.2.

5.2 Study Visits and Procedures

All screened subjects must be identifiable throughout the study. The investigator will maintain a list of all subjects screened with subject numbers and names to enable records to be found at a later date if required. Records up to the time of premature termination or normal study completion should be completed. In the event that a subject is a screen failure (fails after screening visit) or is a run-in failure (withdraws in the run-in period), the primary reason will be recorded.

During the screening visit and pre-randomisation run-in period (Part A), tests and assessments will be performed to check compliance with inclusion/exclusion criteria and study requirements in order to confirm each subjects' eligibility prior to enrolment in Part B.

The screening and pre-randomisation run-in procedures/evaluations detailed in Section 18.1 will be performed during several out-patient visits.

5.2.1 Screening

The subjects will attend the CRU for a screening out-patient visit within 28 days prior to IMP dosing on Day 1.

5.2.1.1 Informed Consent

After a subject has received explanations and responses to his potential questions about the study by the investigator (or designee) and has been given reasonable time read and consider the patient information sheet, a signed and dated informed consent form will be completed with an investigator prior to any study procedures.

5.2.1.2 Screening Procedures

After informed consent is obtained, subjects will be allocated a study-specific subject number which must comply with formatting specifications provided by the sponsor (see Section 3.4.1) and will undergo screening assessments.

5.2.2 Pre-randomisation Run-in Period (Part A)

After successful screening of medical eligibility and within 21 days maximum before IMP dosing on Day 1, subjects will come back to the CRU for an injection test 1 visit, they will receive a pre-randomisation run-in number and be injected in a double blind fashion with either local anaesthetic (lidocaine) or placebo (saline).

They will be assessed for pain perception on site and then be discharged from the CRU from 1 hour post-injection test 1 and continue to record their NRS score at home as described in Section 9.1.2. They will be contacted by telephone by the site to check their safety and collect

their NRS score post-injection test 1 at the end of the injection test 1 day and on the following day.

Approximately one week later and within 14 days maximum before IMP dosing on Day 1, they will come back to the CRU for injection test 2. They will be crossed over and injected with the other agent.

They will be assessed for pain perception on site and then be discharged from the CRU from 1 hour post-injection test 2 and continue to record their NRS score at home as described in Section 9.1.2. They will be contacted by telephone by the site to check their safety and collect their NRS score post-injection test 2 at the end of the injection test 2 day and on the following day. After completion of subject's injection test 2, the blind will be broken by an investigator to check if the subject is a responder.

Subjects will be considered as responders and randomised to Part B if:

- The pattern of pain relief is sufficiently greater with lidocaine than saline using the formula below:
  $[NRS_{predose} - NRS_{1\ hour\ post\text{-}injection\ test}]_{placebo} - [NRS_{predose} - NRS_{1\ hour\ post\text{-}injection\ test}]_{lidocaine} \geq 2$
- The pattern of pain relief is clinically plausible in the investigator's opinion, e.g. onset of pain relief reported by 30 min from time of completing the injections, pain scores after the lidocaine injection test rising again by 2-8 hours post-injection,
- The investigator has no concern regarding compliance with study procedures and safety.

Albeit considered unlikely, should the results be equivocal, or if an unexpected but plausible pattern of response emerges, the decision as to whether a subject should proceed in the study, will be adjudicated by mutual agreement of the investigator and the sponsor.

Subjects will be contacted by telephone by an investigator to inform them of the result. If subjects are assessed as responders and there are no concerns over subject safety, compliance with study assessments, they will enter in Part B.
The scheduled dates should be with sufficient time between study visits test 1, test 2 and baseline. This is to permit the scar area to return to baseline after examination, test dosing or QST procedures.

5.2.3 Randomised Double-blind Period (Part B)

5.2.3.1 Baseline visit

A QST (including light touch, pressure, temperature as stimuli) [stimulus-evoked NRS] and completion of QoL questionnaire SF-36 will be performed within 7 days prior to Day 1. Subjects will also receive a training on how to use their Actiwatch® (device to be used for collection of the spontaneous NRS score). They will start to enter their NRS scores in their Actiwatch®, and will be provided with a paper diary as a back-up solution for NRS score collection.

5.2.3.2 Randomised Period

The subjects will be required to attend the CRU on several occasions during the study:

- On Day 1 in the morning, based on investigator judgement, some of the screening/run-in assessments may be redone to confirm that subjects are still compliant with the inclusion/exclusion criteria and study restrictions. If the subject is considered as stable in pain perception from the screening visit, subjects will undergo pre-dose safety

assessments and then receive the dose of IMP. After IMP dosing, subjects will undergo post-dose assessments as described in Section 18.1.

They will be instructed to continue entering their NRS score in the Actiwatch® and will be provided with a paper rescue medication diary to note their post-dose rescue medication intake (i.e. for scar pain) and NRS score immediately before intake at home (details on rescue medication are provided in Section 6.2).

They will be discharged after a minimum of two hours post-dosing.

- Out-patient visits: Subjects will be required to come back to the CRU for out-patient visits on Week 6 and Week 12.

During the randomised double-blind period (Part B), subjects will also be contacted by telephone by the CRU every day up to Day 7 (subjects might visit the CRU if required for safety purpose) and every two weeks after IMP dosing for collection of AEs, concomitant medications and compliance with pain assessments and other study requirements.

The outpatient visits and calls from Week 2 post-dosing can occur +/- three days around the scheduled date.

5.2.4 Early Discontinuation or End of Study Visit

Subjects will be discharged from the study after completion of an EoS visit for follow-up assessments which will happen 16 weeks after the IMP dosing +/- three days or earlier in case of early discontinuation (ED). The principal investigator will inform the family doctor and pain clinic (if applicable) with details of participation in the clinical study and any relevant information which may help the treating physician in the management of their patient.

5.3 Lifestyle Restrictions

5.3.1 Diet

As poppy seeds can cause a positive result on the drug of abuse (DOA) test, subjects will be advised to avoid eating poppy seeds/food containing poppy seeds for at least 24 hours before attending any DOA test. Subjects diet is expected to remain stable for the duration of the study.

5.3.2 Alcohol

Subjects should abstain from alcohol for 24 hours prior to each visit to the CRU. Excessive alcohol consumption (>21 units per week) should be avoided for the duration of the study.

5.3.3 Physical Activity

Subjects should not change their exercise regime from screening until completion of the study.

5.3.4 Prohibited Concomitant Medications and non Drugs Therapies

The following medications and therapies should not be started during the study:

- Physiotherapy,
- Transcutaneous electrical nerve stimulation therapy,
- Antidepressants and anxiolytics,
- Anticonvulsant medication used to treat pain,
- Opioids

- Non steroidal anti-inflammatory drugs except for brief periods of treatment (up to two days) for other pain or fever,
- Acetylsalicylic acid (aspirin) except for low doses taken for cardioprotection or brief periods of treatment (up to two days) e.g. for episodes of fever,
- Corticosteroids (injected to treat the scar pain),
- Local anaesthetics (injected to treat the scar pain, unless for the pre-randomisation run-in period),
- Medications listed in the exclusion criteria.

Rescue medication (as detailed in Section 6.2, i.e. paracetamol up to 4000 mg per day in divided doses which can be substituted by co-codamol 30 mg/500 mg for the first week post-IMP administration) is allowed except within 12 hours before QST assessments. Subjects must not take medication containing paracetamol and rescue medication without having discussed this with the investigator.

Subject will also be cautioned on the use of any other medication (over-the-counter or prescription containing paracetamol e.g. Lemsip®).

5.4 Priority Order on Study Procedures

The following priority order should be followed in case study procedures are scheduled at the same timepoint:

(1) NRS,
(2) Vital signs,
(3) Physical examination,
(4) ECG,
(5) Blood sampling,
(6) QST,
(7) Actiwatch® training.

6 TREATMENT OF SUBJECTS

6.1 Study Drug(s)

6.1.1 Dosage Form and Strength

Preparation of the agents and IMP will be described in the pharmacy manual.

6.1.1.1 Agents for the Pre-randomisation Run-in Period (Part A)

The agent is a solution for subcutaneous injections (0.5 mL per injection site) of either lidocaine or placebo (saline). A dose of 2.5 mg of lidocaine will be injected per injection site.

Active doses are prepared extemporaneously at the CRU pharmacy with a marketed lidocaine hydrochloride 0.5% v/w solution for injection in 10-mL ampoules.

Placebo doses are prepared extemporaneously at the CRU pharmacy with a sterile and preservative-free sodium chloride solution 0.9% v/w solution for injection (saline) 10-mL ampoules.

The pharmacist preparing the injection syringe will be unblinded as lidocaine and placebo saline ampoules are different in appearance.

After preparation the placebo injection syringe is indistinguishable from the active lidocaine and will be appropriately labelled for immediate use.

The pharmacist will prepare 5 mL of lidocaine or placebo to inject 0.5 mL per injection site with a maximum of 10 injections in the scar pain area.

6.1.1.2 IMP for the Randomised Double-blind Period (Part B)

The IMP is a solution for single intradermal injection (0.2 mL per injection site) of either Dysport or placebo.

Active doses are prepared extemporaneously at the CRU pharmacy with marketed Dysport 500 U powder for solution for injection reconstituted and further diluted with saline to reach the targeted dose as indicated on the Dysport/placebo vial.

Placebo doses are prepared extemporaneously at the CRU pharmacy with a placebo powder for solution for injection reconstituted and further diluted with saline using the same procedure as for the corresponding Dysport dose. They are indistinguishable from the active (Dysport) formulation after reconstitution.

The pharmacist preparing the injection syringe will be blind on the treatment group and unblinded on the dose.

The pharmacist will prepare 2 mL of Dysport/placebo solution to inject 0.2 mL per injection site with a maximum of 10 injections in the scar pain area.

6.1.2 Supplies

The CRU will be provided with:

- Part A: Pre-randomisation run-in kits containing all material for injection test 1 and injection test 2 (lidocaine, lidocaine placebo (saline), injection syringes, injection syringes labels, needles).
- Part B: Randomisation kits (with the white label) and replacement kits (with the blue label) containing all material for Day 1 injection (Dysport or Dysport placebo, ampoules of saline for dilution, injection syringes, injection syringes labels, needles).

lidocaine, lidocaine placebo (saline), Dysport and Dysport placebo will be supplied with lot number, expiry date, certificate of analysis and certificate of compliance or corresponding documentation for the release of the agent and IMP.

6.1.3 Packaging and Labelling

Pre-randomisation run-in kits, randomisation and replacement kits, lidocaine, lidocaine placebo (saline), Dysport and Dysport placebo will be provided in box, vials or ampoules, labelled according to applicable regulations requirements and national laws in force.

6.1.4 Storage

The investigator, or an approved representative (e.g. pharmacist), will ensure that all agents, IMP and any other study-related materials are stored in a secured area, under recommended temperature monitored storage conditions, in accordance with applicable regulatory requirements.

Pre-randomisation run-in kits for Part A (lidocaine and lidocaine placebo (saline)) should be stored between +15°C and +25°C.

Randomisation kits for Part B (Dysport, Dysport placebo and saline used for Dysport/placebo reconstitution) should be stored between +2°C and +8°C.

6.1.5 Dispensing, Treatment and Administration Procedure

All agents and IMP provided to the CRU pharmacist will be allocated and dispensed by appropriately trained staff. Agents and IMP injections will occur under medical supervision.

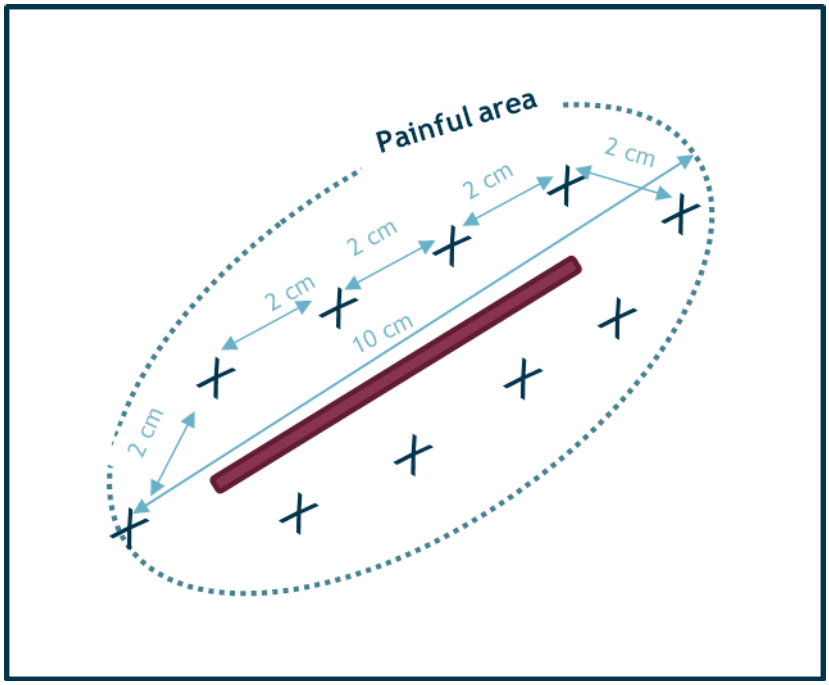
Subcutaneous injections will be performed under a standard volume of 0.5 mL for lidocaine and lidocaine placebo.

Intradermal injections will be performed under a constant volume of 0.2 mL for Dysport and Dysport placebo.

A maximum of 10 sites will be injected in the scar pain area.

The scar pain area reported by the subject will be mapped and drawn on the skin with a skin marker pen. The longitudinal axis of the painful area will be measured. The boundary of the spontaneous pain felt by the subject as well as the sites for injection at 2-cm intervals and starting 1 cm from the edge of the longitudinal axis of the pain area will be marked as represented in Figure 3. A photograph will be recorded with a ruler for scale and used to reproduce the administration scheme on injection test 1, injection test 2 and dosing on Day 1.

Figure 3 Administration Scheme



6.1.6 Accountability

The investigator (or designee) will ensure adequate records (allocation, disposition, shipment, dispensing and returned drugs) are maintained in an agent and IMP accountability log.

6.2 Rescue Medication

Paracetamol (acetaminophen), taken orally as required, is the rescue pain medication during the randomised double-blind period (Part B) and will be provided by the CRU to the subject. It can be taken up to four times a day and should not exceed a daily dose of 4000 mg in divided doses. A single dose of rescue medication is defined as 1000 mg (two tablets).

The single paracetamol dose may be lowered to 500 mg (one tablet) if the investigator/subject feels that the dose is higher than what may be required to provide adequate analgesic effect.

For the first week, in Part B post-dose, the investigator may substitute paracetamol with co-codamol (30 mg/500 mg, maximum 4000 mg of paracetamol per day).

If the subject takes the maximum rescue medication dose of 4000 mg paracetamol per day for three consecutive days and still reports uncontrolled scar pain, the investigator should consider discontinuing the subject from the study. If uncontrolled pain elsewhere in the body were to develop, the management of this should be handled on a case-by-case basis.

The rescue medication should be swallowed whole with water and must not be broken or crushed.

The subject will be cautioned on the use of any other medication (over-the-counter or prescription containing paracetamol e.g. Lemsip®).

Rescue medication should not be taken in conjunction with other analgesic medication unless discussed with the investigator.

If rescue medication is taken, an AE and the corresponding rescue medication should be recorded in the eCRF.

The sponsor medical monitor should be contacted if further guidance is required. For questions on concomitant medications prescribed prior to study participation, the sponsor medical monitor should be contacted before the subject is included in the study.

6.3 Concomitant Medications

Any prior or concomitant medication given to a subject 30 days prior to dosing and during the study will be reported in the eCRF. Dose and trade name will be recorded. The dose of the concomitant medications taken during the randomised double-blind period should be kept constant, where possible, until the EoS.

All medications not prohibited by the protocol and considered necessary for the subject's welfare may be administered and/or continued under the supervision of the investigator.

Only analgesia medication which has been stable during the previous month prior to entry into the study will be allowed.

6.4 Subject Compliance Monitoring

The investigator will be responsible for monitoring subject compliance.

7 SAFETY ASSESSMENTS

The following safety parameters will be collected and reviewed during the study at specific timepoints as described in the study schedule of assessments in Section 18.1:

- AEs,
- Concomitant medications,
- Medical and surgical history,
- Physical examination (including height, body weight, body temperature, examination of the scar at the injection sites),
- Vital signs (including heart rate (HR), and diastolic (DBP) and systolic blood pressures (SBP).

Further routine medical assessments or any additional safety procedures may be performed during the study, if warranted and agreed upon between the sponsor and the investigator, or when clinically indicated.

The investigator will be responsible for a clinical assessment of the study participants during the whole participation of the subjects in the study, from informed consent up to discharge from the study, and for the set up of a discharge plan if needed.

Every effort should be made to ensure that all safety evaluations are completed by the same individual who made the initial baseline determination.

The sponsor medical monitor and the GPS physician will monitor safety data throughout the course of the study.

Any new clinically significant finding should be recorded as an AE from the time informed consent is given.

7.1 Adverse Events

Adverse events will be monitored and reviewed regularly by the sponsor from the time that a subject gives informed consent and throughout the study, and will be elicited by direct, nonleading questioning or by spontaneous reports.

7.1.1 Definition of an Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a preexisting-medical condition, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, ECG).

An AE can include an undesirable medical condition occurring at any time, even if no agent or IMP has been administered.

This definition includes events occurring from the time of the subject giving informed consent until the EoS/ED.

7.1.2 Adverse Events Categorisation, Recording, and Follow-up

For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE (i.e. agent or IMP administration, study procedure or other illness). The investigator is required to assess causality and record that assessment in the eCRF.

Adverse events will be classified by the investigator as mild, moderate or severe according to the following criteria:

- **Mild**: Symptoms do not alter the subject's normal functioning,
- **Moderate**: Symptoms produce some degree of impairment to function, but are not hazardous, uncomfortable or embarrassing to the subject,
- **Severe**: Symptoms definitely hazardous to well-being, significant impairment of function or incapacitation.

The relationship of an AE to agent or IMP administration will be classified by the investigator according to the following:

- **Related**: Reports including good reasons and sufficient information (e.g. plausible time sequence, dose-response relationship, pharmacology) to assume a causal relationship with agent or IMP administration in the sense that it is plausible, conceivable or likely,
- **Not related**: Reports including good reasons and sufficient information (e.g. implausible time sequence and/or attributable to concurrent disease or other drugs) to rule out a causal relationship with agent or IMP administration.

7.1.2.1 Assessment of Expectedness

The expectedness of an AE shall be determined by the sponsor according to the latest approved version of the Dysport Investigator's brochure (IB) and the lidocaine SmPC in the UK (Marketing authorisation number CCI [redacted]).

7.1.2.2 Follow-Up of Adverse Events

Any AEs already recorded and designated as "continuing" should be reviewed at each subsequent assessment.

If an AE is still present at the end of the study, reasonable follow-up clinical monitoring (and up to 30 days after the end of the study) should be managed by the investigator or any appropriate physician until the event or its sequelae resolves or stabilises at an acceptable level, as judged by the investigator. The frequency of follow-up evaluation is left to the investigator's discretion.

7.1.2.3 Reporting of Adverse Events

Any AE considered related to agent or IMP administration that the investigator becomes aware of after completion of the EoS/ED visit must be reported to the sponsor and will be recorded in the corresponding database.

7.1.3 Serious Adverse Event Assessment and Reporting to Sponsor

The investigator must pursue and obtain adequate information to determine the outcome of the AE and to assess whether it meets criteria for classification as an SAE requiring immediate notification to the GPS department of the sponsor.

An SAE is any AE that:

- Results in death,
- Is life-threatening, that is any event that places the subject at immediate risk of death from the event as it occurs. It does not include an event that, had it occurred in a more severe form, might have caused death,
- Results in in-patient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons,

- Hospitalisation is defined as any in-patient admission (even if less than 24 hours). For chronic or long term in-patients, in-patient admission also includes transfer within the hospital to an acute/intensive care in-patient unit,
- Prolongation of hospitalisation is defined as any extension of an in-patient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by the investigator or treating physician. For protocol-specified hospitalisation in clinical studies, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment emergent, clinical AE (i.e. not associated with the development of a new AE or worsening of a pre-existing condition) may meet criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to the sponsor,
- Preplanned or elective treatments/surgical procedures should be noted in the subject's screening documentation. Hospitalisation for a preplanned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae which meet the criteria for seriousness described above,

- Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions,
- Results in congenital anomaly/birth defect in the offspring of a subject who received the agent or IMP,
- Is an important medical event that may not result in death, be life-threatening, or require hospitalisation when, based upon appropriate medical judgement, may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalisation, or the development of drug dependency or drug abuse.

All SAEs regardless of treatment group or suspected relationship to agent or IMP must be reported immediately (**within 24 hours** of the investigator's knowledge of the event) using the fax number specified on the front page of the current document.

Any appropriate means of notification may be used. If the immediate report is submitted by telephone, this must be followed by detailed written reports using the SAE report form.

The following information is the minimum that must be provided to the sponsor:

- Study number,
- CRU,
- Subject number,
- AE,
- Causality,
- Investigator's name and contact details.

The additional information included in the SAE form must be provided to the sponsor or representative as soon as it is available. The investigator should always provide an assessment of causality for each event reported to the sponsor. Upon receipt of the initial report, the sponsor will ask for the investigator's causality assessment if it was not provided with the initial report.

The investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications.

7.1.4 Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the latest approved Dysport IB or the lidocaine SmPC in the UK and that the investigator identifies as related to agent or IMP or procedure.

7.1.5 Pregnancy

Investigators are instructed to report any pregnancy within 24 hours of first awareness of the pregnancy. Information regarding any pregnancy must be collected on the AE page of the eCRF and also on the standard pregnancy outcome report form. Ipsen will request further information from the investigator concerning the course and the outcome of the pregnancy (including the medical condition of the mother, fetus and neonate) using the form.

Information received on any pregnancy with conception date within the time interval specified in the study protocol will be reported in the final clinical study report.

7.1.6 Adverse Events of Special Interest

The effects of Dysport and all BTX products may spread from the area of injection to produce symptoms consistent with BTX effects. These symptoms have been reported hours to weeks after injection. Remote spread of toxin that affects swallowing and breathing can be life threatening, and there have been reports of death. The risk of symptoms is increased in subjects who have underlying conditions (e.g. disorders of the neuromuscular junction) that would predispose them to these symptoms. Dysport is contraindicated in individuals with known hypersensitivity to any BTX preparation or to any of the components in the formulation. Adverse events of special interest (AESIs) for Dysport are AEs that suggest a possible remote spread of effect of the toxin or hypersensitivity. A list of preferred terms of AESIs will be provided in the statistical analysis plan (SAP). All AEs will be monitored by the sponsor to determine if they meet the criteria of AESIs. These AESIs will be further analysed to determine if there is a plausible possibility that they represent distant spread of toxin or hypersensitivity. In order to perform the analysis, variables including alternate aetiology (medical history, concomitant medication, or diagnosis which could account for the symptoms), location of Dysport administration, and temporal relationship to Dysport administration will be considered by the sponsor.

7.1.7 Deaths

All AEs resulting in death during the study period must be reported as a SAE.

The convention for recording death is as follows:

- AE term: Lead cause of death (e.g. multiple organ failure, pneumonia, myocardial infarction),
- Outcome: Fatal.

The only exception is if the cause of death is unknown (i.e. sudden or unexplained death), in which case the AE term may be “death” or “sudden death”.

7.1.8 Reporting to Competent Authorities, IECs/IRBs and other Investigators

The sponsor will ensure that processes are in place for submission of reports of SUSARs occurring during the study to the Competent Authorities (CAs), Independent Ethics Committees

(IECs)/Institutional Review Boards (IRBs) and other investigators concerned by the agent or IMP.

Reporting will be done in accordance with the applicable regulatory requirements.

The sponsor must report all SUSARs to European Medicines Agency's EudraVigilance database within 15 days. Fatal and life-threatening SUSARs should be reported within seven calendar days, with another eight days for completion of the report.

The sponsor can prepare additional reports for other authorities (e.g. FDA).

7.2 Specific Safety Assessments

The investigator is responsible to monitor subjects' safety at any time during the study.

For each assessment performed, the investigator must document his review of the result(s) in the source document(s). In case of abnormal result or value(s) falling outside of predefined normal ranges, the investigator should specify whether the finding is considered as "clinically significant" (CS) or "not clinically significant" (NCS).

Any finding, whether judged CS or NCS may lead to retest at the discretion of the investigator.

7.2.1 Physical examinations

Physical examinations including height, body weight, body temperature (only at screening) and pain description will be conducted as presented in the schedule of assessments in Section 18.1.

Physical examination includes inspection of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, vascular system, extremities, musculo-skeletal system and nervous system.

The nature of the scar pain will be assessed using standardised descriptors e.g. sharp, dull, aching, burning, shooting, stabbing, electric shocks.

Any changes from baseline in physical examination findings judged to be clinically significant by the investigator/ will be recorded as AEs. Any physical examination findings (abnormalities) persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

7.2.2 Vital Signs

Vital signs, including HR, SBP and DBP will be assessed as presented in the schedule of assessments in Section 18.1.

SBP, DBP and HR assessments will be performed with an automated device so that measurements are independent of the observer. These parameters will be recorded after at least 5 minutes rest in supine position for supine assessment, followed by 1 minute in sitting position before standing up where applicable. The standing assessment will be performed after at least 2 minutes standing (only at screening visit). The investigator will record any clinically significant abnormal value as AEs. All AEs will be discussed regularly with the sponsor.

7.2.3 Electrocardiograms

Twelve-lead computerised standard ECGs, with paper printout, will be obtained while the subject is in resting supine position for at least five minutes and until four regular consecutive

complexes are available, at the screening visit only as presented in the schedule of assessments in Section 18.1.

The ECG will be interpreted by a qualified physician at the CRU as soon after the time of ECG collection as possible, and ideally while the subject is still present, for immediate subject management. The qualified physician will document his review and interpretation (including evaluation of clinical significance in case of abnormality) on every ECG printout.

The paper printouts will be kept in the source documents at site. Only the interpretation and abnormalities will be reported in the eCRF for integration with other clinical study data. These paper ECGs may be subject to further review, if appropriate. The investigator will review each safety laboratory test results, document the review, and record any clinically significant abnormal value as AEs. All AEs will be discussed regularly with the sponsor.

7.2.4 Clinical laboratory tests

Blood and urine samples collection will be performed for standard clinical laboratory tests, including biochemistry, haematology, serology and urinalysis panels, as well as specific tests such as urine drug screening and urine pregnancy tests for women of childbearing potential, as indicated in the schedule of assessments in Section 18.1.

Full details related to the samples processing, labelling, storage, shipment and destruction procedures will be documented in a laboratory stand-alone document.

The results of laboratory tests performed during the screening phase must be obtained before injection test 1.

The investigator will review each safety laboratory test results, document the review, and record any clinically significant abnormal value as AEs. All AEs will be discussed regularly with the sponsor.

7.2.4.1 Blood Analyses

Parameters to be assessed are listed in Section 18.3.

7.2.4.2 Urinalysis

Freshly voided urine samples (at least 10 mL) will be collected to perform a dipstick assessment of the parameters listed in Section 18.3. In case of abnormal result on the dipstick, a confirmatory analysis or additional assessments might be requested to the local laboratory, at the discretion of the investigator.

Microscopy will be performed, if indicated, but results will not be collected in the eCRF. If in the opinion of the investigator there are any clinically significant abnormalities in microscopy, they will be recorded as an AE in the eCRF.

7.2.4.3 Pregnancy Test

Human chorionic gonadotrophin will be assessed using an urinary dipstick in all female subjects as specified in the schedule of assessments in Section 18.1. It may be repeated at any time during the study according to investigator's judgement.

7.2.4.4 Drug of Abuse

Urine drug screen testing will be performed as specified in Section 18.1 and at any time at the discretion of the investigator. If positive the subject may still continue in the study if there is a

clinically plausible reason for the result and no concerns by the investigator e.g. a positive opioid test due to the subject taking as prescribed an opioid containing compound as analgesic.

7.2.5 Scar Ultrasound

An ultrasound of the scar will be performed to exclude subjects exhibiting a neuroma in their scar-related painful area.

8 PHARMACOKINETIC ASSESSMENTS

Not applicable.

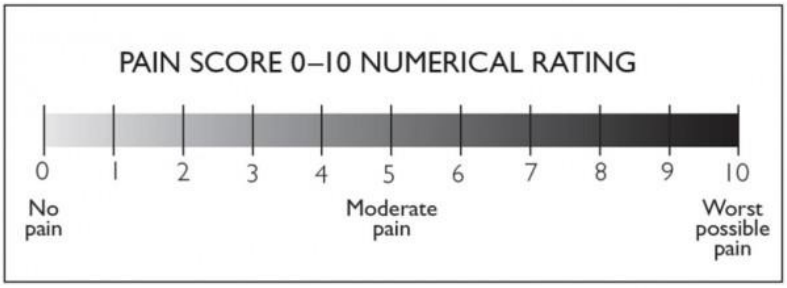
9 PHARMACODYNAMIC ASSESSMENTS

The following pharmacodynamic parameters will be collected and reviewed during the study at specific timepoints as described in the study schedule of assessments in Section 18.1.

9.1 Numerical Rating Scale

The NRS is a 11-point scale to assess subject pain perception as described in Figure 4. Subjects will be asked for their score.

Figure 4 Numerical Rating Scale



9.1.1 Spontaneous Average and Worst Pain NRS Score during the Screening Visit

Subjects will be asked to record their average scar-related pain intensity for the previous 24 hours. The subjects will be asked the following question:

"Please rate your pain by selecting the one number that best describes your pain on average during the last 24 hours."

Subjects will be asked to record their worst scar-related pain intensity for the previous 24 hours. The subjects will be asked the following question:

"Please rate your pain by selecting the one number that best describes your pain at its worst during the last 24 hours."

9.1.2 Spontaneous Current Pain NRS Score in Part A

On the day of the injection test, before the injection test (predose), subjects will be asked what are their current NRS score, the pain felt by the subject at the time of the assessment. The subjects will be asked to answer the following question:

"Please rate your pain by selecting the one number that best describes how much pain you have right now."

Subjects will then be injected and will report their pain relief within 30 minutes after the injection test if any. Subjects will be asked for their current NRS score at 30 minutes and one hour post-injection test, according to the question just described previously.

Subjects will be provided with a paper diary after injection tests 1 and 2. They will be invited to record at home after discharge their current NRS scores hourly up to eight hours and between 20 and 24 hours post-injection test in this diary.

9.1.3 Spontaneous Average and Worst Pain NRS Score in Part B

If subjects are responders, they will be provided with an Actiwatch® during an Actiwatch® training visit to record their spontaneous NRS score at home. They will start NRS score recording from the training visit on Actiwatch® use.

The Actiwatch® will alarm and alert the subjects twice a day to record their average and maximal NRS scores over the preceding 12 hours. The questions will be asked of the subject by the Actiwatch®:

"Please rate your pain by selecting the one number that best describes your pain on average during the last 12 hours."
"Please rate your pain by selecting the one number that best describes your pain at its worst during the last 12 hours.

The Actiwatch® will allow electronic NRS score collection and storage from the Actiwatch® training to EoS. Data will be extracted from the Actiwatch® at each visit. A paper diary will also be provided to subjects in the unlikely event of an Actiwatch® malfunction during the collection period. One week before post-dosing visit to the CRU, the subjects might be requested to complete the paper diary as a quality control check for the data in the Actiwatch® and as a back up in case there is a problem with downloading information from the Actiwatch®.

9.2 Stimulus-evoked NRS Score during Quantitative Sensory Testing

Subjects will be submitted to stimuli of various nature applied to the painful area. Stimulus-evoked NRS score will be collected during the assessments.

Subjects will be asked what are their current NRS scores predose and post-stimulus.

At baseline and at the post-dose visits light touch, pressure and temperature will be used as stimuli for QST.

The QST battery of tests is described in full in Sections 18.4 and 18.5.

9.2.1 Light Touch

The surface of the painful area will be measured on radial spokes starting from the previously mapped painful area applying a von Frey filament. The filament will be applied until it slightly bends and be left in place for 4-5 seconds. Subjects will be asked to report when the von Frey filament first begins to cause any pain sensation and the distance of that point from the initial mapped painful area will be recorded.

The first painful position will be located on the skin and this process will be done for each radial spoke.

The resulting points will then be transferred onto a tracing paper sheet and connected to define the outline of the painful area submitted to light touch. The area of pain will be calculated by using 1 cm^2 squares on the tracing paper (see Section 9.3).

9.2.2 Pressure (Pressure Pain Threshold)

An evoked current NRS score will be recorded for each pressure intensity. The pressure pain threshold (PPT) assesses the level of pressure causing pain. In post-surgical neuralgia subjects, light, normally non-painful pressure applied at the most painful point causes/may cause intense pain. The PPT is assessed by the investigator by using a pressure algometer (contact area 1 cm^2), documented in the source data, and transferred to the eCRF. The threshold for pressure induced pain is measured and then repeated in three series of slowly increasing stimulus intensities (at a rate of about 50 kPa/s). The subject must not be able to look at the readings during the

measurement. For the final PPT, the arithmetic mean of all three consecutive measurements will be calculated (Maier et al., 2010; Mainka et al., 2014).

9.2.3 Temperature

A thermal stimulation will be provided from a thermode placed on the painful area.

The temperature of the thermode is controlled by a Medoc TSA II NeuroSensory Analyser (Medoc Ramat Yishai, Israel). The TSA-II – NeuroSensory Analyser is a precise, computer-controlled device capable of generating and documenting response to highly repeatable thermal and stimuli, such as warmth, cold, heat-induced pain and cold-induced pain. The thermal sensory testing element measures the thresholds for four sensory sub-modalities:

- Warm sensation, for normal subjects, usually at 1- 2ºC above adaptation temperature (C fiber mediated sensation),
- Cold sensation, for normal subjects, usually at 1- 2ºC below adaptation temperature (A-delta fibers mediated sensation),
- Heat induced pain, threshold around 45ºC (mostly C fiber mediated sensation, with some involvement of A-delta fibers).

Cold induced pain, the most variable and difficult to assess of all previous modalities, at about 10º C (combination of both C and A-delta fiber mediated sensation).Warm detection and heat pain thresholds will be determined. The start of the temperature will be 32°C and gradually ramped by 1°C/sec. The heat pain threshold will be obtained when the subject will experience a painful feeling. The thermode will automatically shut down at a preset temperature of 53°C in order to avoid any tissue damage.

Cold detection and cold pain thresholds will also be determined, as programmed by the TSA II.

9.3 Area of Pain

The scar pain area reported by the subject will be mapped and drawn on the skin with a skin marker pen.

The longitudinal axis of the painful area and the total painful area will be measured. The boundary of the spontaneous pain felt by the subject as well as the sites for injection at 2-cm intervals and starting 1 cm from the edge of the longitudinal axis of the pain area will be marked as represented in Figure 3 in Section 6.1.5. A photograph will be recorded with a ruler for scale and used to reproduce the administration scheme on injection test 1, injection test 2 and IMP dosing on Day 1.

10 EXPLORATORY ASSESSMENTS

The following exploratory assessments will be performed during the study at specific timepoints as described in the study schedule of assessments in Section 18.1.

10.1 Quality of Life questionnaire Short Form-36

The SF-36 is a 36-item, subject-reported survey of subject health. The SF-36 consists of eight scaled scores (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health). The higher the score the less disability.

10.2 Rescue Medication

Details on the rescue medication are provided in Section 6.2.

Subjects will be provided with a rescue diary (paper) to record each rescue medication intake, dose, each pain increase (AE), start and stop date and time and current NRS score just before the rescue medication is taken.

If rescue medication is taken, an AE and the corresponding rescue medication should be recorded in the eCRF.

11 STATISTICAL ANALYSES

11.1 Analyses Populations

The following populations will be used for statistical analyses:

- Screened population: All subjects screened (i.e. who signed the informed consent),
- Run-in population: All subjects who received at least one injection in the pre-randomisation run-in period (Part A),
- Randomised population: All subjects randomised in the double-blind period (Part B),
- Safety population: All subjects who received at least one dose of the study drug during the randomised double-blind period (Part B),
- Per protocol (PP) population: All subjects from the randomised population for whom no major protocol deviation occurred.

11.2 Sample Size Calculation

No prospective calculations of statistical power is made.

An appropriate sample size cannot be determined statistically as no previous human data from previous clinical trials are available. A sample size of six subjects per dose of Dysport has been selected. Approximately 24 subjects will be randomised in the double-blind period. Subjects who withdraw within the six first weeks from dosing will be replaced.

11.3 Statistical Methods

A SAP describing the planned statistical analysis in detail with tables, figures, and listings (TFLs) templates will be developed as a stand-alone document.

An overview of the main analysis strategy is provided in the following sections.

TFLs will be presented by treatment group (placebo, Dysport 2.5, 10 and 20 U). Some tables will also be described by total dose received in the painful injection area and the total dose received in the painful area divided by the painful area. This will be fully detailed in the SAP.

11.3.1 Safety Evaluation

11.3.1.1 Pre-randomisation Run-in Period (Part A)

Only listings will be provided.

11.3.1.2 Randomised Double-blind Period (Part B)

Descriptive statistics will be calculated on the safety parameters. No formal statistical tests of safety parameters are planned.

All AEs will be coded according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment emergent AEs (TEAE) summaries will include the overall incidence (by system organ class and preferred term), events by maximum intensity, events by relationship to study drug, events leading to discontinuation of study drug, and SAEs.

Physical examination findings, vital signs, ECG recordings and clinical laboratory parameters will be summarised descriptively at each timepoint. Actual and change from baseline data will be calculated and summarised where data are available. The investigator's interpretation of 12-lead ECGs will be listed.

Concomitant medications will be coded by using the latest version of the World Health Organisation (WHO) drug dictionary and will be summarised with the number and percentage of subjects receiving concomitant medication by drug class and preferred drug name.

Demographic variables (age, height, weight and body mass index) and medical and surgical history will be summarised.

11.3.2 Pharmacokinetic Evaluation

Not applicable.

11.3.3 Pharmacodynamic/ Efficacy Evaluation

11.3.3.1 Pre-Randomisation Run-in Period

Only listing on NRS data will be provided.

11.3.3.2 Randomised Double-blind Period

Analysis of the primary endpoints

Four endpoints have been defined to meet the study primary objective. They are presented in Table 3 with their associated estimate and estimand.

Table 3 Primary Objective - Analysis of Primary Endpoints

Objective	Assessments	Endpoints	Estimate of treatment effect	Estimand
To describe the pharmacodynamic analgesic profile of intradermal doses of Dysport in subjects with abdominal or thoracic chronic scar pain.	Worst pain and average pain within the last 12 hours as assessed by the spontaneous NRS score.	Time to onset, i.e. time to decrease from baseline of two points in the spontaneous NRS score.	The number (%) of subjects who reach the time to onset in each treatment group. The mean time to onset in each treatment group.	For each estimate, the associated estimand will be based on "treatment policy" strategy (i.e. regardless of the intake of rescue medication).
		Peak-effect, i. e. maximal decrease from baseline in the spontaneous NRS score.	The mean peak in each treatment group.	
		Time to peak-effect, i.e. time to reach the peak-effect.	The mean time to reach the peak-effect in each treatment group.	
		Duration of effect, i.e. duration between time to onset and last timepoint with change from baseline in the spontaneous NRS score is ≥2 points.	The mean duration of effect in each treatment group (for the subjects who reach the time to onset).	

Only descriptive statistics will be provided. No statistical test will be performed.

As described in the above table, the estimand will be based on “treatment policy” strategy, which is the estimate of the treatment effect regardless of whether the subject has an intercurrent event during the study.

The following potential intercurrent events will be considered:

- The short-term use of rescue medication,
- The change in use of rescue medication.

Supplementary and sensitivity analysis will be performed to take into account these intercurrent events and to handle missing data. These analysis will be detailed in the SAP.

Analysis of the secondary endpoints

Endpoints have been defined to meet the study secondary objectives. They are presented in Table 4 with their associated estimate and estimand.

Table 4 Secondary Objectives - Analysis of Secondary Endpoints

Objective	Assessments	Endpoints	Estimate of treatment effect	Estimand
To compare the efficacy of intradermal doses of Dysport to placebo.	Spontaneous pain as assessed by the spontaneous NRS score.	Change from baseline in the spontaneous NRS score to each scheduled timepoint.	Difference between each Dysport doses and the placebo group, in the mean change from baseline in the spontaneaous NRS score to each scheduled timepoint.	For each estimate, the associated estimand will be based on "treatment policy" strategy (i.e. regardless of the intake of rescue medication).
	Stimulus-evoked pain as assessed by the NRS score during QST.	Change from baseline in the stimulus-evoked NRS score to each scheduled timepoint.	Difference between each Dysport doses and the placebo group, in the mean change from baseline in the stimulus-evoked NRS score to each scheduled timepoint.	For each estimate, the associated estimand will be based on "treatment policy" strategy (i.e. regardless of the intake of rescue medication).
To assess the safety and tolerability of a range of intradermal doses of Dysport	Refer to Section 11.3.1.			

Only descriptive statistics will be provided. No statistical test will be performed. Supplementary and sensitive analysis will be performed to take into account the intercurrent event and to handle missing data. These analysis will be detailed in the SAP.

Exploratory efficacy endpoints

Endpoints have been defined to meet the study exploratory objectives. They are presented in Table 5 with their associated estimate and estimand.

Table 5 Exploratory Endpoints - Analysis of Exploratory Endpoints

Objective	Assessments	Endpoints	Estimate of treatment effect	Estimand
To explore improvement of QoL using SF-36 questionnaire.	QoL assessed by the SF-36.	Change from baseline in SF-36 scores at each scheduled timepoint (scores/domain that will be used will be described in the SAP).	Difference between each Dysport doses and the placebo group in the SF-36 scores at each scheduled timepoint.	For each estimate, the associated estimand will be based on "treatment policy" strategy (i.e. regardless of the intake of rescue medication).
To explore concomitant use of rescue medication (analgesia).	Use of rescue medication during the study.	- Amount of rescue medication taken during the study. - Time to first intake of rescue medication.	- Difference between each Dysport doses and the placebo group, in amount of rescue medication intake during the randomised double-blind period. - Difference between each Dysport doses and the placebo group, in the time to first intake of rescue medication during the randomised double-blind period.	

Only descriptive statistics will be provided. No statistical test will be performed.

11.3.4 Interim Analyses

No interim analyses are planned for this study.

12 DATA HANDLING AND RECORD KEEPING

12.1 Data Collection

In compliance with GCP, the source data, i.e. medical records/medical notes, etc, should be clearly marked and permit easy identification of a subject's participation in the specified clinical study.

Source data identification and location will be specified in a stand-alone document signed by the investigator(s).

The investigator must record all data relating to protocol procedures, study drug administration, laboratory data, safety, pharmacodynamic/efficacy data on the source documents and report requested data on electronic eCRFs provided for the study (see Section 12.2).

To ensure accurate, complete, and reliable data, the sponsor or its representative will provide instructional material to the study site(s), as appropriate. Training session will be given during a start-up/initiation meeting for instructions on the completion/data entry of any source data documents and eCRF.

The investigators or their designees must verify that all data entries in the eCRF are accurate and consistent with source data records . If certain information is not available for a particular timepoint and/or subject, specific instructions should be followed, e.g. to document that the procedure was either not done or not applicable.

12.2 Data Reporting

Electronic data capture will be utilised for collecting subject data. The study site is required to have a computer and internet connection available for study site entry of clinical data. All entries in the eCRF will be made under the electronic signature of the person performing the action. This electronic signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the handwritten signature. Only sponsor authorised users will have access to the eCRF as appropriate to their study responsibilities. Users must have successfully undergone software application training prior to entering data into the eCRF.

12.3 Data Management

Details of all data management procedures, from the initial planning to the archiving of final datasets/documents following database freeze/lock will be documented in appropriate stand-alone data management and validation plan(s).

Data management will be conducted by a contract research organisation (CRO) approved by the sponsor. All data management procedures will be completed in accordance with the sponsor and contracted CRO standard operating procedures (SOPs). Prior to data becoming available for processing at the assigned data management CRO, they will be monitored. Data documentation removed from the CRU will be tracked by the CRO and the monitor.

The sponsor will ensure that an appropriate eCRF is developed to capture the data accurately and that suitable queries are raised to resolve any missing or inconsistent data. At the end of the study, the investigator will receive the data from the clinical study in an electronic format (PDF files), which will be an exact copy of the eCRF, and will include the full audit trail, for archiving purposes and future reference.

Any queries generated during the data management process will also be tracked by the contracted data management CRO. It is the central study monitor's responsibility to ensure that all queries are resolved by the relevant parties.

The CRO will also ensure, via SAE reconciliation, that SAE data collected in the eCRF are consistent with SAE data held in the sponsor's GPS department (and vice versa).

The coding of an AE, medical history, surgical procedures and concomitant medication terms will be performed by a contracted CRO, managed by the sponsor's Biometry department, and reviewed and approved by the sponsor. Concomitant medications will be coded using WHODRUG-B3 and AEs/medical history terms will be coded using MedDRA.

Only data from enrolled subjects will be reported in the eCRFs and collected in the sponsor's database.

For screen failure subjects, at least the Unique Subject Identifier, the date of informed consent signature, the reason for screen failure and the potential AEs will be reported in the eCRFs and collected in the sponsor's database.

For run-in failure subjects , at least all data recorded for screen failure subjects will be collected in addition to NRS data and previous/concomitant medications.

12.4 Record Keeping

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes.

During the prestudy and initiation visits, the monitor must ensure the archiving facilities are adequate and archiving/retention responsibilities of the investigator have been discussed.

Study documents should be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 15 years) or at least two years have elapsed since the formal discontinuation of clinical development of the product. However, these documents should be retained for a longer period if required by applicable regulatory requirements or by an agreement with the sponsor. The investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing out the study site. The sponsor will inform the investigator, in writing, as to when these documents no longer need to be retained.

If the principal investigator relocates or retires, or otherwise withdraws responsibility for maintenance and retention of study documents, the sponsor must be notified (preferably in writing) so that adequate provision can be made for their future maintenance and retention.

13 REGULATORY AND ETHICAL CONSIDERATIONS

13.1 Regulatory Considerations

The study will be conducted in compliance with IECs/IRBs, informed consent regulations, the Declaration of Helsinki and ICH Guidelines related to GCP. Any episode of noncompliance will be documented. The electronic data capture (EDC) system will comply with the FDA, 21 CFR Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials.

In addition, the study will adhere to all applicable international and local regulatory requirements.

All or some of the obligations of the sponsor will be assigned to a CRU or a CRO.

An identification code assigned to each subject will be used in lieu of the subject's name to protect the subject's identity when reporting AEs and/or other trial-related data (see Section 3.4.1).

13.2 Ethical Review Considerations

The following documents should be submitted to the relevant ethics committee(s) (EC) for review and approval to conduct the study (this list may not be exhaustive):

- Protocol/amendment(s) approved by the sponsor,
- Currently applicable IB or package labelling,
- Relevant investigator's curriculum vitae,
- Subject information and informed consent document(s) and form(s),
- Subject emergency study contact cards,
- Recruitment procedures/materials (advertisements), if any.

The EC(s) will review all submission documents as required, and a written favourable opinion for the conduct of the study should be made available to the investigator before initiating the study. This document must be dated and clearly identify the version number(s) and date(s) of the documents submitted/reviewed and should include a statement from the EC that they comply with GCP requirements.

The study may begin at the investigative site(s) only after receiving this dated and signed documentation of the EC approval or favourable opinion.

During the study, any update to the following documents will be sent to the EC either for information, or for review and approval, depending on how substantial the modifications are: (1) IB; (2) reports of SAEs; (3) all protocol amendments and revised informed consent(s), if any.

At the end of the study, the EC will be notified about the study completion.

13.3 Subject Information Sheet and Consent

The investigator is responsible for ensuring that the subject understands the potential risks and benefits of participating in the study, including answering, orally and/or in writing, to any questions the subject may have throughout the study and sharing any new information that may be relevant to the subject's willingness to continue his or her participation in the study in a timely manner.

The subject information sheet and consent document will be used to explain the potential risks and benefits of study participation to the subject in simple terms before the subject is entered

into the study, and to document that the subject is satisfied with his/her understanding of the study and desires to participate.

The investigator is ultimately responsible for ensuring that the EC-approved informed consent is appropriately signed and dated by each subject prior to the performance of any study procedures. Informed consent obtained under special circumstances may occur only if allowed by local laws and regulations.

13.4 Final Report Signature

The investigator or designee will be proposed to review and sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusion of the report.

14 INSURANCE AND FINANCE

14.1 Insurance

The sponsor declares that it has taken out a product liability insurance covering all subjects screended and enrolled in this study in respect to risks involved in the study.

14.2 Financial Agreement

Since this study is to be performed in partnership with a CRO, separate financial agreements between the sponsor and the CRO on one side, and the CRO and the CRU on the other side, will be signed prior to initiating the study, outlining overall sponsor and investigators responsibilities in relation to the study.

15 QUALITY CONTROL AND QUALITY ASSURANCE

To ensure accurate, complete, and reliable data, the sponsor or its representatives will provide instructional material to the study sites, as appropriate. A start-up training session will be done prior to screening start to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRF, and all study procedures.

15.1 Protocol Amendments and Protocol Deviations and Exceptions

15.1.1 Protocol Amendments

In the event that an amendment to this protocol is required, it will be classified into one of the following three categories:

- Non-substantial amendments are those that are not considered 'substantial' (e.g. administrative changes) and as such only need to be notified to the IECs or regulatory authorities for information purposes.
- Substantial amendments are those considered 'substantial' to the conduct of the clinical study where they are likely to have a significant impact on:
  - the safety or physical or mental integrity of the subjects,
  - the scientific value of the study,
  - the conduct or management of the study,
  - or the quality or safety of the study drug used in the study.

  Substantial amendments must be submitted to and approved by the IECs and relevant regulatory authorities, according to local regulations, prior to implementing changes.
- Urgent amendments are those that require urgent safety measures to protect the study subjects from immediate hazard and as such may be implemented immediately by the sponsor with subsequent IECs and regulatory authority notification, forthwith.

The principal investigator and the sponsor will sign the protocol amendment.

15.1.2 Protocol Deviations and Exceptions

Protocol deviations are defined and classified as either major or minor for a given study. Major deviations (or a combination of minor becoming major) may or may not impact on the analysis population. All minor and major protocol deviations will be identified and recorded by CRU personnel and should be traceable.

Major Protocol Deviation Definition

Any changes in the study design, study conduct and/or procedures that are not in accordance with the protocol and any study materials originally approved by the IEC and which may affect the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

Minor Protocol Deviation Definition

Any changes in the study design, study conduct and/or procedures that are not in accordance with the protocol and any study materials originally approved by the IEC but that do not have an important impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

As a matter of policy, the sponsor will not grant exceptions to protocol-specific entry criteria to allow subjects to enter a study. If under extraordinary circumstances such action is considered ethically, medically, and scientifically justified for a particular subject, prior approval from the sponsor is required before the subject will be allowed to enter the study.

If investigative CRU personnel learn that a subject who did not meet the protocol eligibility criteria was entered in a study (eligibility criteria deviation), they must immediately inform the sponsor. Such subjects will be discontinued from the study, except in exceptional circumstances, following review and written approval by the sponsor.

15.1.3 Information to Study Personnel

The investigator is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, both before starting any study procedures and during the course of the study (e.g. when new staff become involved).

The investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. These study staff members must be listed on the CRU authorisation form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study staff, including the investigator, and for ensuring their compliance with the protocol. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

15.2 Monitoring

The investigator is responsible for the validity of all data collected at the site.

The sponsor is responsible for monitoring these data to verify that the rights and well-being of subjects are protected, study data are accurate (complete and verifiable to source data), and that the study is conducted in compliance with the protocol, GCP, and regulatory requirements.

Before the study initiation visit, the sponsor assigned study monitor will write a monitoring plan indicating the monitoring procedures and at which occasions during the study monitoring visits will be performed.

Periodic visits will be made to the study site throughout the study at mutually agreeable times. Any appropriate communication tools will be set up to ensure the sponsor and/or its representative is/are available for consultation, so they can stay in contact with the study site personnel.

Adequate time and space for monitoring visits should be made available by the investigator.

The investigator will allow direct access to all relevant files (for all subjects) and clinical study supplies (dispensing and storage areas) for the purpose of verifying entries made in the eCRF, and assist with the monitor's activities, if requested.

Quality of the paper-based or electronic data will be reviewed to detect errors in data collection and, if necessary, to verify the quality of the data.

The eCRF is expected to be completed an ongoing basis to allow regular review by the study monitor, both remotely by the internet and during site visits. The study monitor will use functions of the EDC system to address any queries raised while reviewing the data entered by the study site personnel in a timely manner.

Whenever a subject name is revealed on a document required by the sponsor (e.g. laboratory print outs) the name must be blacked out permanently by the site personnel, leaving the date of birth visible, and annotated with the subject number as identification.

15.3 Investigator's Regulatory Obligations

All clinical work under this protocol will be conducted according to GCP rules. This includes that the study may be audited at any time by a quality assurance personnel designated by the sponsor, or by regulatory bodies. The investigator must adhere to the GCP principles in addition to any applicable local regulations.

If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable EC with direct access to any original source documents.

The investigator(s) should demonstrate due diligence in recruitment and screening of potential study subjects. The enrolment rate should be sufficient to complete the study as agreed with the sponsor. The sponsor should be notified of any projected delays, which may impact the completion of the study.

15.3.1 Audit and Inspection

Authorised personnel from external CAs and the sponsor's authorised quality assurance personnel may carry out inspections and audits.

15.3.2 Data Quality Assurance

Monitored eCRFs shared between the investigational site and Data Management CRO will be reviewed (Data Review) for completeness, consistency, legibility and protocol compliance.

Reasons should be given in the relevant eCRF for any missing data and other protocol deviations. Any electronic queries and items not adequately explained will require additional electronic manual queries to be raised to the investigator for clarification/correction. The investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

16 PUBLICATION POLICY

The sponsor encourages acknowledgement of all individuals/organisations involved in the funding or conduct of the study, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the sponsor.

The results of this study may be published or communicated to scientific meetings by the investigators involved in the study. For multicentre studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the study investigators or a steering committee. The sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or paper before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the sponsor and authors (or the author's institution). Requested amendments will be incorporated by the author, provided they do not alter the scientific value of the material.

If patentability would be adversely affected by publication, this will be delayed until (i) a patent application is filed for the content of the publication in accordance with applicable provisions of the clinical trial agreement concerned, (ii) the sponsor consents to the publication, or (iii) the time period as may be agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the sponsor and authors (or authors' institution) after receipt of the proposed publication by the sponsor, whichever of (i), (ii) or (iii) occurs first.

The author undertakes to reasonably consider the sponsor's request for delay to the proposed publication should the sponsor reasonably deem premature to publish the results obtained at the then stage of the study.

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18 ATTACHMENTS

18.1 Attachment 1 – Study Schedule of Assessments

Study Procedures	Screening D-28 max	Injection test 1 D-21 max	Injection test 2 D-14 max	Baseline from D-7 max	D1 pre-dose	D1 post-dose	D2-D7	W2 [a]	W4 [a]	W6 [a]	W8 [a]	W10 [a]	W12 [a]	W14 [a]	W16 EoS/ ED [a]
Part	**Screening**	**Part A**		**Part B**											
Informed consent	X														
Clinic visit	X	X	X	X	X					X			X		X
Subject call		X [b]	X [b]	X [c]			X [d]	X [d]	X [d]		X [d]	X [d]		X [d]	
Eligibility check	X			X	X										
Demography	X														
Medical and surgical history	X														
Drug of abuse	X														
Urine pregnancy test (female subjects only)	X				X										X
Physical examination	X			X	X					X [f] [g]					X
Vital signs	X [e]	X [g]	X [g]	X [g]	X [g]	X [g]				X [g]					X [g]
ECG, Safety lab	X														
Scar ultrasound	X														
Painful area mapping	X	X	X	X	X [h]					X			X		X

Study Procedures	Screening D-28 max	Injection test 1 D-21 max	Injection test 2 D-14 max	Baseline from D-7 max	D1 pre-dose	D1 post-dose	D2-D7	W2 [a]	W4 [a]	W6 [a]	W8 [a]	W10 [a]	W12 [a]	W14 [a]	W16 EoS/ ED [a]
Pre-randomisation Part A		X													
Lidocaine/placebo injection (saline)		X	X												
NRS score collection and diary providing		X [i]	X [i]												
Actiwatch® training and providing				X											
Randomisation in Part B					X										
Dysport/placebo injections					X										
Spontaneous NRS	X [j]	X [k]	X [k]	X [l]	X [l]	X [l]	X [l]	X [l]	X [l]	X [l]	X lk]	X [l]	X [l]	X [l]	X [l]
Rescue medication diary provided						X									
Reminder about analgesia washout 12-hour period pre-injections or QST		X	X	X	X			X	X	X	X	X	X	X	
QST (stimulus-evoked NRS)				X [m]						X [m]			X [m]		
QoL (SF-36)				X						X			X		
Concomitant medications and adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a Visit to be performed ± 3 days around the scheduled date.

b In the evening and on the following morning to check safety and collect spontaneous NRS scores.

c Once the NRS scores from injection tests 1 and 2 are known and blind has been broken, the subject's responder status is determined. Subjects will be contacted by telephone by an investigator to inform of the result, and in the case of responders, they will enter in Part B.

d Subjects will be contacted by telephone by the CRU every day up to Day 7 and every 2 weeks after IMP dosing for collection of AEs, concomitant medications and compliance with pain assessments and other study requirements.

e Vital signs in both standing and supine position.

f Includes an examination of the scar at injection sites.

g Vital signs in supine position only.

h Just before the IMP dosing.

i Subjects will be provided with a paper diary after injection tests 1 and 2. They will be invited to record at home after discharge their current NRS scores hourly up to 8 hours and between 20 and 24 hours post-injection test in this diary.

j Subjects will be asked what were their average and worst NRS scores within 24 hours before the visit.

k Subjects will be asked what is their current NRS score pre-injection test. They will report their pain relief within 30 minutes after the injection test if any. They will be asked for their current NRS score at 30 minutes and 1 hour post-injection test. They will be discharged home and collect their current NRS scores hourly up to 8 hours and between 20 and 24 hours post-injection test.

l The Actiwatch® will alarm and alert the subjects twice a day to record their worst and average NRS scores over the preceding 12 hours. The Actiwatch® will allow electronic NRS score collection and storage from the Actiwatch® training to EoS. Data will be extracted from the Actiwatch® at each visit.A paper diary will also be provided to subjects in the unlikely event of an Actiwatch® malfunction during the collection period. One week before post-dosing visit to the CRU, the subjects might be requested to complete the paper diary in case of Actiwatch® malfunction or data quality check.

m QST (light touch, pressure, thermal) to be performed before D-3, at week 6 and week 12. Predose NRS score is the current pain.

18.2 Attachment 2 – Blood Sampling Summary

This table summarises the maximum number of (veni) punctures and blood volumes for all blood sampling (screening safety laboratories) during the study.

Fewer venipunctures and blood draws may actually occur if needed for safety purposes, but this will not require a protocol amendment.

Purpose	**Maximum Blood volume per sample (mL)**	**Maximum Number of Blood Samples**	**Maximum Total Volume (mL)**
Screening			
Clinical laboratory tests : Haematology, biochemistry and serology	25	1	25
Provision for repeat tests (local lab)	10	1	10
Total over	**35**	**Approximately 35 mL**	

18.3 Attachment 3 – Clinical Laboratory Tests

Haematology	Clinical Chemistry	Serology
Erythrocyte count	Alanine aminotransferase	Hepatitis B surface antigen
Haematocrit	Albumin	Hepatitis C virus ribonucleic acid
Haemoglobin	Alkaline phosphatase	Human immunodeficiency virus
Leukocyte count	Aspartate aminotransferase	
Mean cell haemoglobin	Bicarbonate	
Mean cell haemoglobin concentration	Calcium	
Mean cell volume	Chloride	
Absolute counts of: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils • Platelets	Conjugated bilirubin	
	Creatinine	
	Creatine kinase	
	C-reactive protein	
	Gamma-glutamyl transferase	
	Glucose (fasting)	
	Phosphorus	
	Potassium	
	Sodium	
	Total bilirubin	
	Total cholesterol	
	Total protein	
	Triglycerids	
	Urea	

Urinalysis (dipstick)	Specific Parameters
Bilirubin	Urine drug screen, including at least amphetamines, methamphetamines, benzodiazepines, cocaine, opiates, tetrahydrocannabinol and barbiturates
Blood	Urine pregnancy test (women of childbearing potential)
Glucose	Urine pregnancy test (women of childbearing potential)
Ketones	
Microscopic examination of sediment (if indicated)	
Nitrite	
pH	
Protein	
Urobilinogen	

18.4 Attachment 4 – Quantitative Sensory Testing

Quantitative Sensory Testing Procedure Guideline (QST)

St Pancras Clinical Research	
Prepared by:	PPD
Checked by:	PPD
Approved by:	PPD

1. Document owner

St Pancras Clinical Research (SPCR)

2. Affected parties

All trained staff performing QST at SPCR.

3. Purpose

The purpose of this SOP is to provide detailed instructions for performing QST in a structured manner by a trained staff in order to get consistent and reproducible results.

4. Scope

For all staff who are suitably trained to perform QST at SPCR.

5. Definitions

Sensory Threshold (ST): ST is the weakest stimulus that a subject can detect.

Pain Perception Threshold (PPrT): PPrT is the lowest intensity of a painful stimulus at which the subject perceives pain.

Static Mechanical Allodynia (SMA): SMA is the response to light sustained normally innocuous pressure against the skin.

Dynamic Mechanical Allodynia (DMA): DMA is the response to a normally innocuous light moving mechanical stimulus on the skin.

Temporal summation (TS): TS is a condition, which demonstrates an increased perception of pain to repetitive painful stimuli.

Pressure Pain Threshold (PPT): PPT is the minimum force applied (pressure) which induces pain.

Conditioned Pain Modulation (CPM), also known as Diffuse Noxious Inhibitory Control (DNIC): CPM refers to an endogenous pain modulatory pathway. This is described as "pain inhibits pain". CPM occurs when a response to a second, often spatially distant, noxious stimuli inhibits the response from a painful stimulus.

Cold Detection Threshold (CDT): CDT is the temperature which is perceived as a ‘change’ when the temperature is decreased from 32 degrees.

Warm Detection Threshold (WDT): WDT is the temperature which is perceived as a 'change' when the temperature is increased from 32 °C.

Cold Pain Threshold (CPT): CPT is the temperature which is perceived as 'painful' when the temperature is decreased from 32 °C.

Heat Pain Threshold (HPT): HPT is the temperature which is perceived as 'painful' when the temperature is increased from 32 °C.

6. Preparation

6.1. Environment:

All tests are performed in comfortable, quite room at room temperature (around 20 °C). Ensure there is a comfortable adjustable couch for the subject to sit or lie down. As some of the tests ideally should be run uninterrupted, it is best to avoid unnecessary distractions or interruptions.

6.2. Equipments: The following equipments are required to perform the QST.

von Frey filaments

Camel hair brush (1cm brush width)

Hand-held pressure algometer (Algometer type II, Somedic Production AB, Sweden, diameter contact tip 10mm; cover 2mm thick rubber; standardised and constant speed of pressure increase of 0.3kg/s)

TSA-II Quantitative NeuroSensory Analyzer; Medoc, Ramat Yishai, Israel

Timer/ stop watch

Sharps container

Alcohol wipes

Marker pen

6.3. Operator and training

The tests should be performed by a single trained operator for each patient.

7. Performing the tests:

Always perform the test in the same order below. Mark/ map the area of painful site for testing and identify the suitable non-painful/ contralateral site for testing. Always do test over the non-painful site and then do the painful site for comparison (unless mentioned otherwise below). Do all tests with the patients eyes closed. Explain to the patient before each test to ensure a consistent response and if required demonstrate the procedure on the patient.

Sensory Threshold (ST): Seventeen, progressively rigid, monofilament, von Frey fibers (filaments represent stimuli from 0.039 – 4386mN) will be used for this test. Test the area with von Frey's filament, starting from the lowest/ thinnest monofilament. Each filament should be applied to the skin at a 90° angle with sufficient force to bend or bow the filament. The filament is held in place for 1.5 seconds and then removed. The exact threshold is found by repetitive testing ascending fibre sizes. The patient is instructed to respond ''Yes'' when a stimulus was felt. Each filament is applied up to 3 times in increasing filament thickness and the patient should say 'Yes' at least twice for the threshold filament.

Pain Perception Threshold (PPrT): This test is performed similar to ST but the response is the monofilament producing discomfort/ pain.

Static Mechanical Allodynia (SMA): This test is performed by applying the plastic base of a von Frey filament for 10 seconds with sufficient pressure, indenting the skin-testing area. This is recorded in a 11-point Numerical Rating Scale (NRS).

Dynamic (Brush evoked) Mechanical Allodynia (DMA): DMA is evoked by gently stroking the test area with a foam brush. This is recorded in a 11-point Numerical Rating Scale (NRS).

Temporal summation: This test is done only on the painful site. A baseline NRS score will be obtained from the patient with the vFF as part of the PPrT measurement. This fibre will be used for the test. The patient is given a repetitive stimulation consisting of 30 repetitions of a pressure stimulus applied for 1 second duration for 30 seconds. The magnitude of the stimulus is set at the level of the subjects' pressure pain threshold. Patients rate the pain intensity on a NRS at the end of the 30 seconds and this is repeated for up to 10 sets or until you or the patient decide to stop due to the level of discomfort.

Pressure Pain Threshold (PPT): A hand-held pressure algometer (Algometer type II, Somedic Production AB, Sweden, diameter contact tip 10mm; cover 2mm thick rubber; standardised and constant speed of pressure increase of 0.3kg/s) is used to measure the PPT's in KPa (Kilo Pascal). The probe is placed perpendicular to the skin and standard incremental pressure is applied until the subject perceived the pressure as pain when the procedure is immediately terminated. At each site, a set of 3 measurements are taken at 4 different nearby points and an average PPT value is calculated from the 12 measurements. If the patient feels too uncomfortable then please restrict to fewest number of consistent readings (3 to 4).

Ischemic arm test to measure DNIC: DNIC is measured by inducing a heterotopic noxious conditioning stimulation. This is evoked by an inflated blood pressure cuff and thereby creating an ischaemic compression of the arm. Blood pressure cuff positioned on the arm was inflated above systolic pressure (200 mmHg) for 10 minutes, or until a Numerical Rating Scale of 6 was achieved. The point on the painful site with the lowest PPT value (average of 3 measurements) is chosen to measure the CPM response. A set of 3 PPT measurements are then taken at this point following which the cuff is deflated. The average of the 3 PPT measurements are taken.

Temperature Thresholds: This test measures the CDT, WDT, CPT and HPT and paradoxical heat sensation. Four sensory sub-modalities are measured using a computer-controlled thermode with surface area of 9 cm2 which is connected to a patient-activated push-button (TSA-II Quantitative NeuroSensory Analyzer; Medoc, Ramat Yishai, Israel). The system contains a pre-loaded software which dictates the temperature changes. The baseline temperature is automatically set at 32 °C. The temperature then decreases at a constant rate of 1 °C /s until the subject perceived the thermode as cold and immediately pressed a push-button. Four consecutive measurements are taken with the thermode returning to baseline temperature each time. Similarly, HDT, is measured but with the temperature increased from 32°C. Subsequently, CPT and HPT are determined in a similar manner, and in that order but by taking an average of 3 consecutive measurements. To avoid thermal injury the thermode with automatically cut off at 0°C at the lower end and at 50°C at the higher end.

8. Termination of QST

Terminate the tests once you have done all the tests as per this SOP or at patients request or if you feel it is inappropriate to continue the test for any reason (such as level of patient discomfort, patient refuses consent, patient psychologically inappropriate, unable to get consistent response or equipment malfunction).

9. Equipment care

It is the operators responsibility to ensure that sufficient care is given while handling the equipment. Disposable sharps should be put in the sharps bin. Please ensure that the non-

disposable equipment, which has a patient contact is cleaned with alcohol swabs and standard hospital infection control policies are adopted.

There is a copy of the equipment available which can be consulted for any clarification.

The algometer needs regular calibration and the thermal equipment needs refilling with distilled water and servicing.

18.5 Attachment 5 – Criteria to be evaluated for each subject

According to Treede

Pain with a distinct neuroanatomically plausible distribution a

A history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system b

Demonstration of the distinct neuroanatomically plausible distribution by at least 1 confirmatory test c

Demonstration of the relevant lesion or disease by at least 1 confirmatory test d

Grading for certainty for the presence of neuropathic pain

Definite neuropathic pain	All (1 to 4)
Probable neuropathic pain	1 and 2, plus either 3 or 4
Possible neuropathic pain	1 and 2 without confirmatory evidence from 3 or 4

A region corresponding to a peripheral innervation territory or to the topographic representation of a body part in the central nervous system.

The suspected lesion or disease is reported to be associated with pain, including a temporal relationship typical for the condition.

As part of the neurologic examination, these tests confirm the presence of negative or positive neurologic signs concordant with the distribution of pain. Clinical sensory examination may be supplemented by laboratory and objective tests to uncover subclinical abnormalities.

As part of the neurologic examination, these tests confirm the diagnosis of the suspected lesion or disease. These confirmatory tests depend on which lesion or disease is causing neuropathic pain.

18.6 Attachment 6 – Protocol Amendment #2 Summary

All additions have been identified by the use of underline and all deletions by ~~strikethroughs~~.

3.1 Overall Study Design and Plan

Before dosing on Day 1, the subjects will perform baseline assessments including a ~~full~~ quantitative sensory testing (QST) assessing allodynia, hyperalgesia and conditioned pain modulation, completion of a QoL questionnaire, and safety assessments (physical examination, vital signs measurements, collection of adverse events (AEs) and recording of concomitant medication).

4.1 Inclusion Criteria

Subjects must fulfil all of the following criteria to be considered eligible for enrolment in the study.

~~(1)~~ (1a) Male and female subjects aged between 18 and ~~65~~ 75 years inclusive at the time of giving informed consent.

(2) Subjects suffering from an area of chronic pain post-abdominal or thoracic surgery, chronic abdominal or thoracic scar pain.

(3) Longitudinal axis of the pain area of 10 cm long maximum (as mapped upon screening).

(4) Subjects with moderate to severe pain, i.e. spontaneous NRS score of 4-8 which has been stable for the previous month before screening.

(5) Stable use of analgesics (or any medication impacting pain perception) during the month before screening and expected to be stable for the study duration.

(6) Under stable medication regimen for other medication, i.e. during the month before screening.

~~(7)~~ (7a) Time from surgery which caused the painful scar more than six months and less than ~~five~~ ten years at screening.

(8) No other distracting pain either chronic or acute.

(9) Female subjects of childbearing potential must have a negative urine pregnancy test result and be willing to use reliable contraceptive measures throughout study participation. Reliable forms of contraception include but are not limited to hormonal contraceptives (e.g. oral, patch, injection), double-barrier (e.g. male condom plus spermicide, or female diaphragm plus spermicide), intrauterine device, male partner has had a vasectomy, total abstinence from intercourse with male partners (periodic abstinence is not acceptable). Female subjects meeting any of the following criteria are not considered to be of childbearing potential: postmenopausal (≥ 47 years of age and amenorrhoeic for at least 12 consecutive months), have been sterilised surgically (e.g. bilateral tubal ligation), have had a hysterectomy, have had a bilateral oophorectomy.

(10) The subject's primary care physician has provided evidence which can be used to confirm that within the last 12 months of dosing that there is nothing in their medical history that would preclude their enrolment into a clinical study.

5.2.2 Pre-randomisation Run-in Period (Part A)

After successful screening of medical eligibility and within 21 days maximum before IMP dosing on Day 1, subjects will come back to the CRU for an injection test 1 visit, they will receive a pre-randomisation run-in number and be injected in a double blind fashion with either local anaesthetic (lidocaine) or placebo (saline).

They will be assessed for pain perception on site and then be discharged from the CRU from 1 hour post-injection test 1 and continue to record their NRS score at home as described in Section 9.1.2. They will be contacted by telephone by the site to check their safety and collect their NRS score post-injection test 1 at the end of the injection test 1 day and on the following day.

Approximately one week later and within 14 days maximum before IMP dosing on Day 1, they will come back to the CRU for injection test 2. They will be crossed over and injected with the other agent.

They will be assessed for pain perception on site and then be discharged from the CRU from 1 hour post-injection test 2 and continue to record their NRS score at home as described in Section 9.1.2. They will be contacted by telephone by the site to check their safety and collect their NRS score post-injection test 2 at the end of the injection test 2 day and on the following day. After completion of subject's injection test 2, the blind will be broken by an investigator to check if the subject is a responder.

Subjects will be considered as responders and randomised to Part B if:

- The pattern of pain relief is sufficiently greater with lidocaine than saline using the formula below:
  $[NRS_{predose} - NRS_{1\ hour\ post\text{-}injection\ test}]_{placebo} - [NRS_{predose} - NRS_{1\ hour\ post\text{-}injection\ test}]_{lidocaine} \geq 2$
- The pattern of pain relief is clinically plausible in the investigator's opinion, e.g. onset of pain relief reported by 30 min from time of completing the injections, pain scores after the lidocaine injection test rising again by 2-8 hours post-injection,
- The investigator has no concern regarding compliance with study procedures and safety.

Albeit considered unlikely, should the results be equivocal, or if an unexpected but plausible pattern of response emerges, the decision as to whether a subject should proceed in the study, will be adjudicated by mutual agreement of the investigator and the sponsor.

Subjects will be contacted by telephone by an investigator to inform them of the result. If subjects are assessed as responders and there are no concerns over subject safety, compliance with study assessments, they will enter in Part B.
The scheduled dates of the subjec't visit should be with sufficient time between study visits test 1, test 2 and baseline. This is to permit the scar area to return to baseline after examination, test dosing or QST procedures.

18.6.1.1 Baseline visit

A ~~full~~ QST (including light touch, pressure, temperature as stimuli) [stimulus-evoked NRS] and completion of QoL questionnaire SF-36 will be performed within 7 days prior to Day 1. Subjects will also receive a training on how to use their Actiwatch® (device to be used for collection of the spontaneous NRS score). They will start to enter their NRS scores in their Actiwatch®, and will be provided with a paper diary as a back-up solution for NRS score collection.

9.2 Stimulus-evoked NRS Score during Quantitative Sensory Testing

Subjects will be submitted to stimuli of various nature applied to the painful area. Stimulus-evoked NRS score will be collected during the assessments.

Subjects will be asked what are their current NRS scores predose and post-stimulus.

At baseline ~~all the tests will be performed. At~~ and at the post-dose visits light touch, ~~only light touch~~ pressure and temperature will be used as stimuli for ~~light~~ QST.

The QST battery of tests is described in full in Sections 18.4 and 18.5.

18.1 Attachment 1 – Study Schedule of Assessments

Study Procedures	Screening D-28 max	Injection test 1 D-21 max	Injection test 2 D-14 max	Baseline from D-7 max	D1 pre-dose	D1 post-dose	D2-D7	W2 [a]	W4 [a]	W6 [a]	W8 [a]	W10 [a]	W12 [a]	W14 [a]	W16 EoS/ ED [a]
Part	**Screening**	**Part A**		**Part B**											
Informed consent	X														
Clinic visit	X	X	X	X	X					X			X		X
Subject call		X [ab]	X [ab]	X [bc]			X [cd]	X [ed]	X [ed]		X [ed]	X [ed]		X [ed]	
Eligibility check	X			X	X										
Demography	X														
Medical and surgical history	X														
Drug of abuse	X														
Urine pregnancy test (female subjects only)	X				X										X
Physical examination	X			X	X					X [ef] [fg]					X
Vital signs	X [dc]	X [fg]	X [fg]	X [fg]	X [fg]	X [fg]				X [fg]					X [fg]
ECG, Safety lab	X														
Scar ultrasound	X														
Painful area mapping	X	X	X	X	X [gh]					X			X		X
Pre-randomisation Part A		X													

Study Procedures	Screening D-28 max	Injection test 1 D-21 max	Injection test 2 D-14 max	Baseline from D-7 max	D1 pre-dose	D1 post-dose	D2-D7	W2 [a]	W4 [a]	W6 [a]	W8 [a]	W10 [a]	W12 [a]	W14 [a]	W16 EoS/ ED [a]
Lidocaine/placebo injection (saline)		X	X												
NRS score collection and diary providing		X [hi]	X [hi]												
Actiwatch® training and providing				X											
Randomisation in Part B					X										
Dysport/placebo injections					X										
Spontaneous NRS	X [ij]	X [jk]	X [jk]	X [kl]	X [kl]	X [kl]	X [kl]	X [kl]	X [kl]	X [kl]	X [kl]	X [kl]	X [kl]	X [kl]	X [kl]
Rescue medication diary provided						X									
Reminder about analgesia washout 12-hour period pre-injections or QST		X	X	X	X			X	X	X	X	X	X	X	
QST (stimulus-evoked NRS)				X [lm]						X [m]			X [m]		
QoL (SF-36)				X						X			X		
Concomitant medications and adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a Visit to be performed ± 3 days around the scheduled date.

ab In the evening and on the following morning to check safety and collect spontaneous NRS scores.

bc Once the NRS scores from injection tests 1 and 2 are known and blind has been broken, the subject's responder status is determined. Subjects will be contacted by telephone by an investigator to inform of the result, and in the case of responders, they will enter in Part B.

~~c~~d Subjects will be contacted by telephone by the CRU every day up to Day 7 and every 2 weeks after IMP dosing for collection of AEs, concomitant medications and compliance with pain assessments and other study requirements.

~~d~~e Vital signs in both standing and supine position.

~~e~~f Includes an examination of the scar at injection sites.

~~f~~g Vital signs in supine position only.

~~g~~h Just before the IMP dosing.

~~h~~i Subjects will be provided with a paper diary after injection tests 1 and 2. They will be invited to record at home after discharge their current NRS scores hourly up to 8 hours and between 20 and 24 hours post-injection test in this diary.

~~i~~j Subjects will be asked what were their average and worst NRS scores within 24 hours before the visit.

~~j~~k Subjects will be asked what is their current NRS score pre-injection test. They will report their pain relief within 30 minutes after the injection test if any. They will be asked for their current NRS score at 30 minutes and 1 hour post-injection test. They will be discharged home and collect their current NRS scores hourly up to 8 hours and between 20 and 24 hours post-injection test.

~~k~~l The Actiwatch® will alarm and alert the subjects twice a day to record their worst and average NRS scores over the preceding 12 hours. The Actiwatch® will allow electronic NRS score collection and storage from the Actiwatch® training to EoS. Data will be extracted from the Actiwatch® at each visit.A paper diary will also be provided to subjects in the unlikely event of an Actiwatch® malfunction during the collection period. One week before post-dosing visit to the CRU, the subjects might be requested to complete the paper diary in case of Actiwatch® malfunction or data quality check.

~~l~~m ~~Full~~ QST (light touch, pressure, thermal) ~~battery~~ to be performed before D-3, week 6 and week 12. Predose NRS score is the current pain.

~~m QST (light touch, pressure, thermal).~~

18.4 Attachment 4 – Quantitative Sensory Testing

Quantitative Sensory Testing Procedure Guideline (QST)

St Pancras Clinical Research	
Prepared by:	PPD
Checked by:	PPD
Approved by:	PPD

1. Document owner

St Pancras Clinical Research (SPCR)

2. Affected parties

All trained staff performing QST at SPCR.

3. Purpose

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5. Definitions

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Pain ~~perception threshold~~ Perception Threshold (PPrT): PPrT is the lowest intensity of a painful stimulus at which the subject perceives pain.

Static ~~mechanical allodynia~~ Mechanical Allodynia (SMA): SMA is the response to light sustained normally innocuous pressure against the skin.

Dynamic Mechanical Allodynia (DMA): DMA is the response to a normally innocuous light moving mechanical stimulus on the skin.

~~Punctate hyperalgesia (PH): PH is a response to a painful stimuli such a pin prick.~~

~~Vibration disappearance threshold (VDD): This is the threshold at which the vibration is not longer detected while testing with 64 Hz graduated Rydel and Seiffer tuning fork.~~

Temporal summation (TS): TS is a condition, which demonstrates an increased perception of pain to repetitive painful stimuli.

Pressure ~~pain threshold~~ Pain Threshold (PPT): PPT is the minimum force applied (pressure) which induces pain.

Conditioned Pain Modulation (CPM), also known as Diffuse Noxious Inhibitory Control (DNIC): CPM refers to an endogenous pain modulatory pathway. This is described as "pain inhibits pain". CPM occurs when a response to a second, often spatially distant, noxious stimuli inhibits the response from a painful stimulus.

Cold Detection Threshold (CDT): CDT is the temperature which is perceived as a ‘change’ when the temperature is decreased from 32 degrees.

Warm Detection Threshold (WDT): WDT is the temperature which is perceived as a 'change' when the temperature is increased from 32 ~~degree~~ °C.

Cold Pain Threshold (CPT): CPT is the temperature which is perceived as 'painful' when the temperature is decreased from 32 ~~degree~~ °C.

Heat Pain Threshold (HPT): HPT is the temperature which is perceived as 'painful' when the temperature is increased from 32 ~~degree~~ °C.

6. Preparation

6.1. Environment:

All tests are performed in comfortable, quite room at room temperature (around 20 °C). Ensure there is a comfortable adjustable couch for the subject to sit or lie down. As some of the tests ideally should be run uninterrupted, it is best to avoid unnecessary distractions or interruptions.

6.2. Equipments: The following equipments are required to perform the QST.

von Frey filaments

Camel hair brush (1cm brush width)

~~Neurotips™~~

~~64 Hz graduated Rydel and Seiffer tuning fork~~

Hand-held pressure algometer (Algometer type II, Somedic Production AB, Sweden, diameter contact tip 10mm; cover 2mm thick rubber; standardised and constant speed of pressure increase of 0.3kg/s)

TSA-II Quantitative NeuroSensory Analyzer; Medoc, Ramat Yishai, Israel

Timer/ stop watch

Sharps container

Alcohol wipes

Marker pen

6.3. Operator and training

~~At~~ The tests should be performed by a single trained operator for each patient.

7. Performing the tests:

Always perform the test in the same order below. Mark/ map the area of painful site for testing and identify the suitable non-painful/ contralateral site for testing. Always do test over the non-painful site and then do the painful site for comparison (unless mentioned otherwise below). Do all tests with the patients eyes closed. Explain to the patient before each test to ensure a consistent response and if required demonstrate the procedure on the patient.

Sensory Threshold (ST): Seventeen, progressively rigid, monofilament, von Frey fibers (filaments represent stimuli from 0.039 – 4386mN) will be used for this test. Test the area with von Frey's filament, starting from the lowest/ thinnest monofilament. Each filament should be applied to the skin at a 90° angle with sufficient force to bend or bow the filament. The filament is held in place for 1.5 seconds and then removed. The exact threshold is found by repetitive testing ascending fibre sizes. The patient is instructed to respond ''Yes'' when a stimulus was felt. Each filament is applied up to 3 times in increasing filament thickness and the patient should say 'Yes' at least twice for the threshold filament.

Pain ~~perception threshold~~ Perception Threshold (PPrT): This test is performed similar to ST but the response is the monofilament producing discomfort/ pain.

Static ~~mechanical allodynia~~ Mechanical Allodynia (SMA): This test is performed by applying the plastic base of a von Frey filament for 10 seconds with sufficient pressure, indenting the skin-testing area. This is recorded in a 11-point Numerical Rating Scale (NRS).

Dynamic (Brush evoked) Mechanical Allodynia (DMA): DMA is evoked by gently stroking the test area with a foam brush. This is recorded in a 11-point Numerical Rating Scale (NRS).

~~Punctate hyperalgesia (PH): This is tested using the blunt end of Neurotips™. Apply the stimulus twice for about half a second, with a 5-second interval between stimuli for each site. This is recorded in a 11-point Numerical Rating Scale (NRS).~~

~~Vibration Disappearance Threshold (VDD): This is tested using a Rydel-Seiffer tuning fork (64 Hz, 8/8 scale) by placing it over a bony prominence closest to the test site.~~

Temporal summation: This test is done only on the painful site. A baseline NRS score will be obtained from the patient with the vFF as part of the PPrT measurement. This fibre will be used for the test. The patient is given a repetitive stimulation consisting of 30 repetitions of a pressure stimulus applied for 1 second duration for 30 seconds. The magnitude of the stimulus is set at the level of the subjects' pressure pain threshold. Patients rate the pain intensity on a NRS at the end of the 30 seconds and this is repeated for up to 10 sets or until you or the patient decide to stop due to the level of discomfort.

Pressure Pain Threshold (PPT): A hand-held pressure algometer (Algometer type II, Somedic Production AB, Sweden, diameter contact tip 10mm; cover 2mm thick rubber; standardised and constant speed of pressure increase of 0.3kg/s) is used to measure the PPT's in KPa (Kilo Pascal). The probe is placed perpendicular to the skin and standard incremental pressure is applied until the subject perceived the pressure as pain when the procedure is immediately terminated. At each site, a set of 3 measurements are taken at 4 different nearby points and an average PPT value is calculated from the 12 measurements. If the patient feels too uncomfortable then please restrict to fewest number of consistent readings (3 to 4).

Ischemic arm test to measure DNIC: DNIC is measured by inducing a heterotopic noxious conditioning stimulation. This is evoked by an inflated blood pressure cuff and thereby creating an ischaemic compression of the arm. Blood pressure cuff positioned on the arm was inflated above systolic pressure (200 mmHg) for 10 minutes, or until a Numerical Rating Scale of 6 was achieved. The point on the painful site with the lowest PPT value (average of 3 measurements) is chosen to measure the CPM response. A set of 3 PPT measurements are then taken at this point following which the cuff is deflated. The average of the 3 PPT measurements are taken.

Temperature ~~threshold~~ Thresholds: This test measures the CDT, ~~HDT~~ WDT, ~~CDP~~ CPT and ~~HDP~~ HPT and paradoxical heat sensation. Four sensory sub-modalities are measured using a computer-controlled thermode with surface area of 9 cm2 which is connected to a patient-activated push-button (TSA-II Quantitative NeuroSensory Analyzer; Medoc, Ramat Yishai, Israel). The system contains a pre-loaded software which dictates the temperature changes. The baseline temperature is automatically set at 32 °C. The temperature then decreases at a constant rate of 1 °C /s until the subject perceived the thermode as cold and immediately pressed a push-button. Four consecutive measurements are taken with the thermode returning to baseline temperature each time. Similarly, HDT, is measured but with the temperature increased from 32°C. Subsequently, CPT and HPT are determined in a similar manner, and in that order but by taking an average of 3 consecutive measurements. To avoid thermal injury the thermode with automatically cut off at 0°C at the lower end and at 50°C at the higher end.

8. Termination of QST

Terminate the tests once you have done all the tests as per this SOP or at patients request or if you feel it is inappropriate to continue the test for any reason (such as level of patient

discomfort, patient refuses consent, patient psychologically inappropriate, unable to get consistent response or equipment malfunction).

9. Equipment care

It is the operators responsibility to ensure that sufficient care is given while handling the equipment. Disposable sharps should be put in the sharps bin. Please ensure that the non-disposable equipment, which has a patient contact is cleaned with alcohol swabs and standard hospital infection control policies are adopted.

There is a copy of the equipment available which can be consulted for any clarification.

The algometer needs regular calibration and the thermal equipment needs refilling with distilled water and servicing.