"FOLLOW THE SUTURES".

AN OPEN MULTICENTER, MULTINATIONAL PILOT STUDY TO EXPLORE TOLERABILITY, SAFETY AND EFFECT OF A NEW PROCEDURE FOR INJECTING BOTULINUM TOXIN IN THE HEAD AGAINST CHRONIC MIGRAINE

Protocol Identification Number: FollowTheSutures

EudraCT Number: 2017-002516-13

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PROTOCOL VERSION NO. 2 - 20-03-2018

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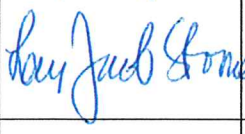
SIGNATURE PAGE

Title	"FollowTheSutures". An open multicenter, multinational pilot study to explore tolerability, safety and effect of a new procedure for injecting botulinum toxin in the head against chronic migraine
Protocol ID no:	FollowTheSutures
EudraCTno:	2017-002516-13

I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:

Name	Title	Role	Signature	Date
Geir Bråthen	Overlege, 1.aman	Sponsor		March 20, 2018
Lars Jacob Stovner	Overlege, professor	Principal investigator		March 20, 2018

PROTOCOL SYNOPSIS

Protocol title: "FollowTheSutures". An open multicenter, multinational pilot study to explore tolerability, safety and effect of a new procedure for injecting botulinum toxin in the head against chronic migraine

Sponsor	Overlege/1.amanuensis Geir Bråthen
Phase and study type	Phase II, interventional study, 2 centres, international (2 countries), open, no controls
Investigational Medical Product (IMP) (including active comparator and placebo) :	Botulinum toxin A
Centers:	Department of Neurology and Clinical Neurophysiology, St. Olavs Hospital, Trondheim Norway Department of Neurology, Mayo Clinic, Scottsdale, Arizona, USA
Study Period:	September 2018 Anticipated recruitment period: 1,5 year Estimated date of last patient completed: May 2020
Treatment Duration:	Expected treatment duration pr. Patient 1 day
Follow-up:	Expected follow-up period pr. Patient 12 weeks

Objectives	Main study objective or hypothesis: Is the new injection procedure safe and tolerable? Key secondary objectives: Indications of a positive effect on the headache Possibility of unblinding in a later controlled and blinded study through side effects Obtain data on variability of main efficacy data for powe calculation of future RCT
Endpoints:	Primary endpoint: Number of adverse events Secondary endpoint: Moderate-severe headache days week 5-8 after injection compared to baseline Ability to make forehead wrinkles after injection
Study Design:	Open-label, non-controlled, single arm, multicenter study.
Main Inclusion Criteria:	– Men or women between 18 and 64 years with chronic migraine, as defined in the ICHD-3 beta version. – Chronic migraine should have been present for at least ½ year prior to evaluation for study inclusion. – For fertile women: Negative urine pregnancy test and use of highly effective contraception – Written informed consent
Main Exclusion Criteria	– Patients with diseases that are contraindications for use of BoNT-A (Myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, other diseases interfering with neuromuscular function) or allergy to BoNT-A – Other primary or secondary headache disorder, including medication overuse headache (MOH). This means that at least one attempt to

withdraw acute medication should have been performed earlier, but without success

- Severe depression or other psychiatric disorder that may interfere with the treatment.
- Abuse of alcohol or illicit drugs
- Use of more than one headache prophylactic medication, or change in type and dose of prophylactic medication < 28 days before start of baseline period
- Previous exposure at any time to any botulinum toxin serotype
- Infection at one or more injection site(s)
- Subject received extracranial nerve block, cervical facet injection, or other interventional procedure for headache within the prior 3 months.
- Use of opioids or barbiturate containing medication(s) ≥ 10 days per month within the preceding 3 months

Sample Size:

40 patients, 20 in Trondheim and 20 in Scottsdale

Efficacy Assessments:

1. Change from baseline in frequency of moderate/severe headache days (main efficacy variable). Moderate-severe headache day defined as headache lasting ≥ 4 hours where pain becomes at least moderate in intensity, or is successfully treated with acute headache medication.
2. Headache responder rate, response defined as ≥ 50 % reduction in moderate/severe headache days, as defined in 1)
3. Migraine responder rate, response defined as ≥ 50 % reduction in migraine headache days
4. Change from baseline in frequency of migraine headache days
5. Change from baseline in frequency of acute headache pain medication intakes (all categories)
6. Change from baseline in frequency of triptan intake

7. Change from baseline in intensity of headache on headache days
8. Change from baseline in headache free days
9. Change from baseline in frequency of moderate/severe headache days week 1-12 after injection

Safety Assessments:	Adverse events (AEs) recorded in headache diary, and at each scheduled and unscheduled contact with study personnel.
Other Assessments:	Cosmetic effects (forehead wrinkles) Duration of injection procedure

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
AE	Adverse Event
BoNT-A	Botulinum toxin A
CM	Chronic migraine
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CTC	Common Toxicity Criteria (for cancer trials only)
CTCAE	Common Terminology Criteria for Adverse Event (for cancer trials only)
DAE	Discontinuation due to Adverse Event
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICHD-3beta	International Classification of Headache Disorders, version 3 beta
IMP	Investigational Medicinal Product (includes active comparator and placebo)
MOH	Medication overuse headache
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Serious Unexpected Adverse Reaction

INTRODUCTION

1.1 Background – Disease

Headaches are among the major public health issues globally. According to the Global Burden of Disease 2013 Study, headache disorders are ranked third on the list of the disorders causing most functional impairment on the population level(4). A large proportion is caused by migraine, affecting around 11% of the population globally(5). Among migraine patients, those with the chronic form (Chronic migraine, CM) are the most affected, and for these patients with headache more than half of the days (and the majority of these with migraine) the quality of life and participation in activities are highly limited.

The treatment of CM patients includes avoidance of headache triggers, optimization of attack treatment, and prophylactic treatments with various medications. However, for a large proportion of patients, standard migraine prophylactic medicines are not effective or well tolerated, and many patients fail to adhere to the prophylactic medication, overuse acute medications and develop medication overuse headache (MOH). For those who start using opioids there may be serious health consequences. Hence, CM constitutes a large global public health issue affecting 0.1 to 1% of the population in most countries, depending on the definition(6).

1.2 Background - Therapeutic Information

Today, CM is treated with acute medication (mostly analgesics, NSAIDs) and prophylactic medication that patients take daily (e.g. beta-blockers, topiramate, valproic acid, candesartan, flunarizine, amitriptyline). Only topiramate has documented effect on CM. In patients with both CM and MOH, discontinuation of acute medication can be very effective, either alone or in combination with prophylactic medication. However, the success rate of prophylactics is relatively low (usually approximately 40 to 50% of patients respond) and quite a few have side effects that may limit their use.

1.3 Pre-Clinical & Clinical Experience with Investigational Medicinal Product (IMP)

During the last 5 years, injection of onabotulinum toxin A (BoNT-A) in pericranial and neck muscles have become an established method of treating CM, and it is currently being used in most hospitals and by many general practitioners all over Norway. The effect in CM was shown in a

pooled analysis of two large studies (PREEMPT 1 and 2)(7-9), including almost 1400 patients who had injections of 5 Units of BoNT-A or placebo in 31 sites in the head and neck, and in addition up to 40 units at different sites of maximal pain. The effect of Botox® was relatively modest, with a reduction in headache days per month of 1.8 days (95%CI 2.5-1.1) compared to placebo. The proportion with at least 50% reduction of headache days was 47% vs 35% in the two groups ($p<0.001$). The fact that many patients develop cosmetic effects in the forehead on treatment with botulinum toxin raises the question of unblinding. In general, the safety and tolerability of the procedure was good. In a pooled analysis of more than 1900 patients in the PREEMPT studies receiving at least 1 dose (mean163 U) BoNT-A to the head and neck, 3 % discontinued due to adverse events (AEs). The most frequent BoNT-A-associated side effects were neck pain (13%), muscle weakness (8%), musculoskeletal stiffness (6%) and eyelid ptosis (5%), Serious AEs (SAEs) occurred in 5.4% of patients receiving BoNT-A and in 3% of those receiving placebo(10). The most frequently reported serious AE was migraine, followed by pneumonia, uterine leiomyoma and headache.

A major disadvantage with BoNT-A treatment for CM is the cost which for the doses of BoNT-A used in the PREEMPT studies amounts to from 12000 -16 000 NOK per year, although some patients may need treatment less often than 4 times every year. An cost-effectiveness analysis of the Institute for Clinical and Economic Review (ICER) (http://icer-review.org/wp-content/uploads/2016/01/CTAF_Migraine_Final_Report_081914-2.pdf) has evaluated that the cost of each headache day averted with BoNT-A is between 157 and 223 dollars, depending on the number of days with migraine per month (20 or 15)(8). Also, each treatment, typically given four times a year, involves many subcutaneous injection sites all over the head and neck (31 to 37) which for these patients who are often hypersensitive are experienced as very painful. In addition, the scientific evidence for the effect is limited (only one study, although a large one), the effect over placebo was relatively small, and the possibility of incomplete blinding may cast doubt on the results.

The pathophysiological mechanism underlying the effect in CM is not clearly understood. Injected into muscles, BoNT-A causes transitory (usually 3 months) impaired neuromuscular transmission with paresis. This effect is mediated by the toxin, which is taken up in nerve terminal of cholinergic motor neurons, and then cleaves one of the so called SNARE proteins (SNAP-25) which is essential for exocytosis of Acetylcholine-containing vesicles. The mechanism for the antinociceptive effect is less clear, but it seems that the substance is also taken up in sensory nerve terminals where it also

cleaves SNAP-25, thus hindering the exocytosis of proinflammatory neuropeptides like CGRP and Substance P which have a role in sensitization of nerve. It also blocks exocytosis of Transient Receptor Potential Vanilloids 1 (TRPV1) channels, involved in acute pain sensation, which are thus not expressed in nerve terminals. While these mechanisms may explain the local effects of BoNT-A, there is in animal models also an antinociceptive effect contralaterally, and even far away from the injection sites which may be explained by a retrograde axonal transport of BoNT-A to the central nervous system where it may have post-synaptic effects(11).

Still, it has been a puzzle how administration of the toxin in the pericranial and neck muscles outside the skull affects migraine headache, which is believed to originate mainly in the brain and meninges and involve pain

Figure 1: Hemisected rat cranium, demonstrating receptive fields both in the dura and the extracranial periosteum of the meningeal spinosus nerve. From (1)

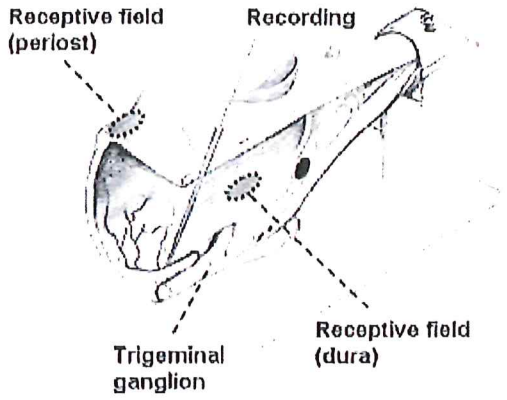
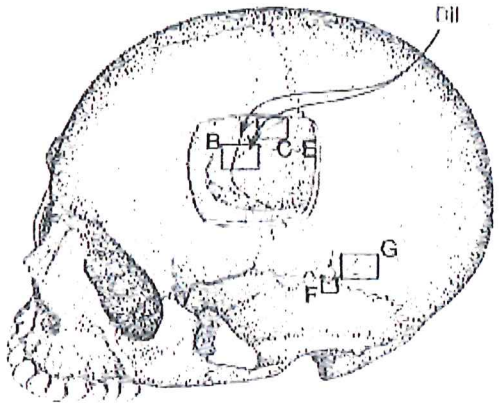


Figure 2: Human cranium, demonstrating DiI tracing of the contralateral dural spinosus nerve through cranial window (BCE) and ipsilateral extracranial course through squamous suture (FG). From (2)



fibers inside the calvarium. An answer to this may be the demonstration of intracranial sensory fibers in the meninges sending off collaterals that pass through the skull bones from inside to outside through the sutures and emissary vein channels, to innervate the periosteum and extracranial muscles, in both mice, rats and humans (1, 2, 12) (Figure 1 and 2).

During the last years, it has been shown that Botulinum toxin A (BoNT-A) can inhibit mechanical nociception in peripheral trigeminal neurons in rodents Burstein, Zhang (13), and that injection of BoNT-A extracranially in the region of the sagittal and lambdoid sutures can suppress nociceptors' responses to stimulation in the meninges (dura mater) (3). The effect of injection near the sutures was more pronounced than when it was injected in the temporalis and neck muscles (Figure 3). This suggests that there may be a more effective way to administer BoNT-A for chronic migraine than the protocol for the PREEMPT studies, namely to "follow the sutures".

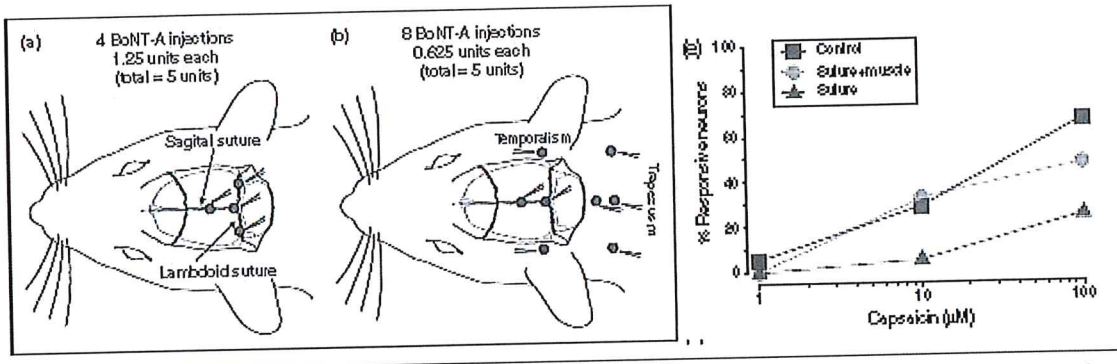


Figure 3: Injection in rat of BoNT-A 5 U extracranially in either a) sutures only, or b) in sutures and neck muscles. Curve shows responsiveness of meningeal afferent C-fibers after sensitization with TRPV1-agonist capsaicin in increasing doses in controls (blue squares), injection in sutures and neck muscles (green circles) or in sutures only (red triangels) . From (3)

1.4 Rationale for the Study and Purpose

There is no doubt that chronic migraine is a large public health problem, which is both disabling and costly. Many patients and headache doctors see BoNT-A treatment as a big stride forward, but it is a problem that the effect has been shown in only one study (and only after pooling of the results from two studies), with a low therapeutic gain, and there was a potential of unblinding due to side effects (14). For this reason, before this costly treatment is expanded to potentially several thousand patients in Norway (conservative estimates is 0.1-0.5 % of the adult population, i-e 4000 to 20 000 patients), it would be highly desirable that 1) there is additional good scientific evidence for use of BoNT-A , 2) a more effective treatment procedure is developed, 3) the potential for unblinding is reduced, and 4) the dose, number of injection sites and cost can be halved (vial of 100U at a price of NOK 2130 instead of a vial of 200 U, NOK 4290), 5) the adverse effects are minimized. We believe this can be the results of this pilot project where we give

injections along the sutures, which can open up for a later randomized, blinded and controlled study.

Risk/benefit analysis: With the proposed procedure, we foresee little risk to the patients, compared with standard treatment, since the BoNT-A dose is smaller and there are fewer injection sites. Based on the standard procedure, the patients may have no effect, and some patients may also get more headache and even a status migrainousis after the injections, in addition to pain at injection sites and some weakening of muscles. The benefits to the patients are fewer injections and less pain, and the new procedure may even have a better effect than the standard procedure. Also, the procedure will be less expensive and time-saving. The potential of unblinding because of side effects is reduced since the new injection protocol does not involve the forehead and the lower neck, reducing the probability of visible cosmetic effects, neck stiffness or weakness. If an effect of the same order of magnitude as in the PREEMPT-studies can be demonstrated and confirmed in a future RCT, this will greatly corroborate the rationale for clinical use of BoNT-A in CM, and it may give lower costs and less injection-site pain. If the effect is better than with the standard procedure, as the animal studies may indicate(3), it can represent a huge benefit for patients and society as a whole.

Rationale for the choice of dose:

5 units per injection site is the same as was used in the PREEMPT study, which has been well tolerated. The argument for the total dose of 90 U (i.e. 18 sites) is mostly that the diffusion of the drug is approximately 2 cm in all directions, implying that if injections are given as shown in the figure the drug will reach almost all the suture lines. Another argument is cost, since it will require less than one vial (100U), and it is therefore cost-saving compared to the standard procedure which requires 155-195 U (2 vials). A third argument is that it may be difficult to get out all of the dissolved drug from the vial, but 90 U will always be possible.

STUDY OBJECTIVES and related endpoints

A placebo-controlled study is needed to demonstrate an effect. The two PREEMPT studies, which in combination showed an effect on the current injection procedure, included > 1900 patients, whereof around 1400 were evaluable. This is a very costly study. Before undertaking a large study, it is highly desirable to perform an open pilot study in a smaller group to 1) evaluate whether the new injection procedure is safe and tolerable to the patients, 2) see whether there is indication of

any effect at, 3) evaluate whether, in a later blinded study, there is the possibility of unblinding through side effects, and 4) obtain data on the variability of the main efficacy data to enable a power calculation for a future RCT.

1.5 Primary Endpoint

- Number of adverse events (AEs).
  These will be recorded in the headache diary (Appendix 1) by the patient and reviewed during the scheduled visits. At each scheduled or unscheduled contact (visit or telephone), patients will be asked an open question about any medical problems that have occurred since the last contact, and these will also be recorded in the CRF. Patients can contact the doctor or study nurse throughout the study. Symptoms or signs that are clearly related to migraine will not be recorded.

Right after the injection the doctor will fill out a form about bleeding and other problems. The patient will indicate on a VAS scale the level of pain of the procedure.

1.6 Secondary Endpoints

- Duration of injection procedure (minutes)
- Cosmetic effects (on forehead wrinkles).
  Patients will be asked at before each consultation to look in the mirror to detect differences in ability to make forehead wrinkles (no, mild, moderate, marked difference, full paralysis).
- Course of headache as recorded in the headache diary (Appendix 1) before and after injection (efficacy variables, derived from the guidelines (18) and allowing comparison with the PREEMPT studies). The baseline period is mainly compared with the weeks 5-8 after the injections (1-6 below).

  1. Change from baseline in frequency of moderate/severe headache days (main efficacy variable). Moderate-severe headache day defined as headache lasting $\geq$ 4 hours where pain becomes at least moderate in intensity.
  2. Change from baseline in headache days headache day defined as headache lasting $\geq$ 4 hours where pain intensity may be mild, moderate, or severe.

3. Change from baseline in frequency of migraine headache days
4. Change from baseline in frequency of acute headache pain medication intakes (all categories)
5. Change from baseline in frequency of triptan intake
6. Change from baseline in frequency of moderate/severe headache days week 1-12 after injection

2 OVERALL STUDY DESIGN

The study is a phase II study (exploration of a new therapeutic approach), open-label, non-controlled, single arm, multicenter study.

Study Period	Estimated date of first patient enrolled: September 1st, 2018
	Anticipated recruitment period: 1.5 years
	Estimated date of last patient completed: May 2020
	End of study (the last visit of the last patient): May 2020
Treatment Duration:	1 day
Follow-up:	12 weeks

3 STUDY POPULATION

3.1 Selection of Study Population

The study will be performed at the outpatient clinics of the neurological departments of two academic hospitals (St. Olavs Hospital, Trondheim, Norway, and Mayo Clinic, Scottsdale, AZ, USA)

3.2 Number of Patients

40 patients will be included in this trial, 20 at St. Olavs Hospital and 20 at the Mayo Clinic.

3.3 Inclusion Criteria

Patients will be recruited from the outpatient clinics, or through advertisements.

All of the following conditions must apply to the prospective patient at screening prior to receiving study agent

1) Patients (men or women) must be between 18 and 64 years with chronic migraine, as defined in the ICHD-3 beta version(17).
2) CM should have been present for at least ½ year prior to evaluation for study inclusion.
3) For women of child-bearing potential (WOCB)[1] there must be a negative urine pregnancy test and use of highly effective contraception[2]
4) Signed informed consent (See Appendix 2, Patient information and consent form) and expected cooperation of the patients for the treatment and follow up must be obtained and documented according to ICH GCP, and national/local regulations.

[1] WOCBP is defined as fertile women, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include: hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. WOCBP will have to agree to take a pregnancy test before inclusion and on the day of the injection, before the injection.

[2]Such methods include: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable); intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomised partner; sexual abstinence. This group of patients should not be using other drugs that might interact and reduce the efficacy of the used anticonceptive drug.

3.4 Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria:

- Patients with diseases that are contraindications for use of BoNT-A (Myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, other diseases interfering with neuromuscular function) or allergy to BoNT-A
- Other primary or secondary headache disorder, including medication overuse headache (MOH). This means that at least one attempt to withdraw acute medication should have been performed earlier, but without success
- Severe depression or other psychiatric disorder that may interfere with the treatment.
- Abuse of alcohol or illicit drugs
- Use of more than one headache prophylactic medication, or change in type and dose of prophylactic medication < 28 days before start of baseline period
- Previous exposure at any time to any botulinum toxin serotype
- Infection at one or more injection site(s)
- Subject received extracranial nerve block, cervical facet injection, or other interventional procedure for headache within the prior 3 months.
- Use of opioids or barbiturate containing medication(s) ≥ 10 days per month within the preceding 3 months
- Participating in another trial that might affect the current study
- In the opinion of the investigator, the patient should not participate (e.g. not able to comply with study procedures).

4 TREATMENT

For this study BoNT-A (Botox®) defined as Investigational Medicinal Product(s) (IMP).

4.1 Drug Identity, Supply and Storage

BoNT-A (Botox®, Allergan) powder, has marketing authorizatrion in both participating countries. A vial of 100U, delivered from the pharmacy. It will be stored according to instructions on the

package leaflet. Just before injections, study personnel will dissolve the content of the vial in 4 ml (cc) of isotone saline water (9 mg/ml), and distribute the solution in 4 syringes.

4.2 Dosage and Drug Administration

The study treatment will be administered to the subject by authorized site personnel only.

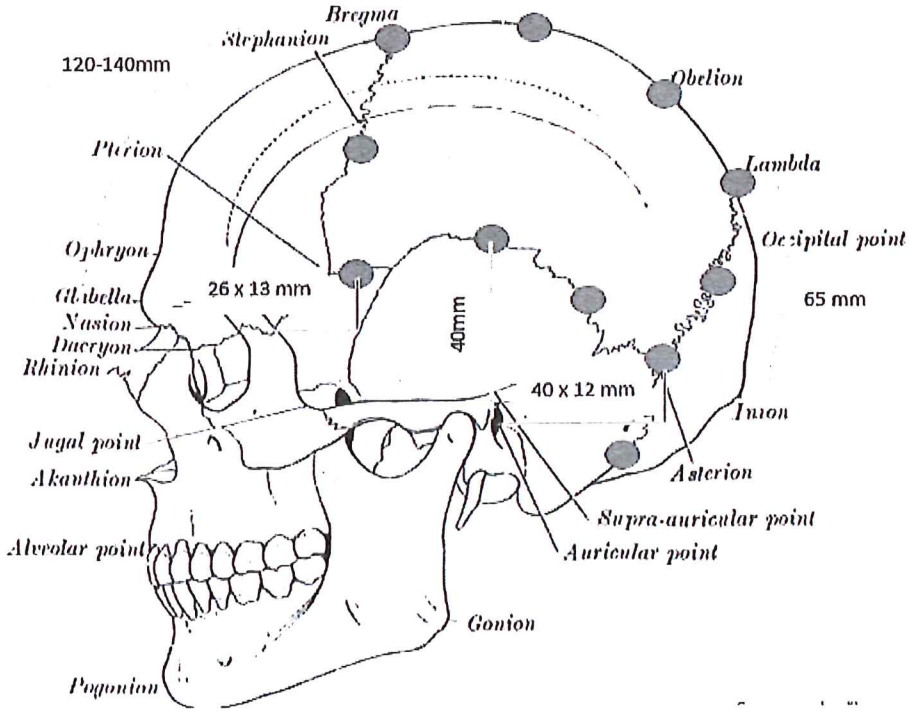
Preparation of BoNT-A: 100 U of Botox® is solved in 4 ml (cc) of isotone saline water (9 mg/ml), distributed in 4 syringes. This is half the usual concentration, allowing for better diffusion in order to reach the target structures.

Injections:

In the study of rat skulls, innervation was particularly dense in the region of the occipitomastoid suture around the attachment of the splenius and longissimus capitis muscles, and in the human skull in the region of the squamous suture, between the parietal bone and the squamous part of the temporal bone(2). However, in these studies, not all sutures were investigated, and in a study on adult mice, a rich innervation by fibers passing from inside to outside the skull has been demonstrated in all sutures (12). On the basis of these observations, the following injection sites for 18 injections of 5U of BoNT-A (total 90U) have been chosen (Figure 4).

5 U (0.2 ml) are injected subcutaneously, and down to but not penetrating the galea aponeurotica, at each site (Figure 4). Needle size: 30 Gauge, 1.3cm length.

Injection sites (Figure 4). (Measurements from (19) if not otherwise stated)



In the midline

1. Bregma (12-14 cm posterior to Nasion)
2. Lambda (6.5 cm above Inion which is easily palpable)
3. 1/3 of distance between Bregma and Lambda
4. 2/3 of distance between Bregma and Lambda

Bilaterally

5. Asterion (4 cm behind and 12 mm above the level of the auricular point)
6. Midway between Asterion and Lambda
7. Apex of squamous suture, 4 cm above Auricular point.
8. Squamous suture, midway between Asterion and 7.
9. Pterion (26 mm behind and 13 mm above the posterolateral margin of the frontozygomatic suture which is palpable) (20)
10. Midway between Pterion and Bregma
11: Occipitomastoid suture (palpable, where caudal part of mastoid process joins occipital bone)

4.3 Duration of Therapy

Injections will be performed only once in each patient.

4.4 Premedication and Monitoring

A negative pregnancy test, taken on the day of injections, must be documented before injections are performed in fertile women (for definition, see 3.3)

4.5 Schedule Modifications

None

4.6 Concomitant Medication

The following medication is not allowed while the patient is included in the study / in the treatment phase of the study:

- More than one headache prophylactic medication, or change in type and dose of prophylactic medication < 28 days before start of baseline period (see exclusion criteria)
- Opioids or barbiturate containing medication(s) ≥ 10 days per month within the preceding 3 months of the study (see exclusion criteria)
- Any botulinum toxin serotype (before or during study).

All concomitant medication (incl. vitamins, herbal preparation and other "over-the-counter" drugs) used by the patient will be recorded in the patient's file and CRF.

4.7 Subject Compliance

Compliance will be evaluated from attendance to visits and keeping of headache diaries.

4.8 Drug Accountability

The drug, which has marketing authoriziation, will routinely be ordered from the pharmacy and dispensed from the pharmacy's own stock.

The drug will be in the department's medicine room in a refrigerator. The medicine will be prepared for injection immediately before the procedure by study personnel. A drug accountability form (Appendix 3) will be kept for all medicines.

Dispensing entries on the Drug Accountability Record Form includes:

- Date and origin of study agent receipt
- Manufacturer and lot number from vial or package
- Date of injection, including the year
- Patient identification number
- Patient's initials
- Dose administered
- Initials of person recording the information

4.9 Drug Labeling

The drug wil not be labelled specificly for this project since it has marketing authorization, and is prepared by study personnel just before administration to the patient.

4.10 Subject Numbering

Each subject is identified in the study by a unique subject number that is assigned when subject signs the Informed Consent Form. Once assigned the subject number cannot be reused for any other subject.

The same primary identifier will be used throughout the study.

5 STUDY PROCEDURES

5.1 Flow Chart

Table 1 Trial flow chart

	Screening Period			Treatment Period		End of study visit	Withdrawal visit
Time	**Inclusion visit 28 days before treatment**	**Telephone 7-14 days after inclusion**	**Treatment visit**	**Telphone 7-14 days after treatment visit**	**Telphone 56-63 days after treatment visit**	**84-91 days after treatment**	**When necessary**
Informed consent	X						
Inclusion/exclusion Evaluation	X		X				
Medical History	X						
Prior treatment	X						
Physical Examination[2)]	X						
Questionnaires (QoL, ...)							
Pregnancy test (fertile women)			X				
Treatment administration			X				

	Screening Period			Treatment Period		End of study visit	Withdrawal visit
Time	**Inclusion visit 28 days before treatment**	**Telephone 7-14 days after inclusion**	**Treatment visit**	**Telphone 7-14 days after treatment visit**	**Telphone 56-63 days after treatment visit**	**84-91 days after treatment**	**When necessary**
Adverse event registering	X	X	X	X	X	X	X
Record of concomitant medication	X	X	X	X	X	X	X
Check of headache diary		X	X	X	X	X	X

5.2 Inclusion visit

Patients are informed about the project, and a medical history is taken, including previous diseases, allergies, medication (previous and present), and a neurological and general medical examination is performed, including blood pressure and pulse measuring. An evaluation of whether inclusion or exclusion criteria apply is made, and if the patient is eligible for the study, the informed consent is signed.

Informed consent

Informed consent must have been given voluntarily by each subject before any study specific procedures are initiated. The following tests will be done at screening:

Clinical status

Medical history (including disease history and corresponding treatment details), physical examination eg. (cor/pulm/), vital signs (blood pressure and pulse).
It will be checked if women are of child-bearing potential, and if so, whether they use highly effective contraception (Definitions, see 3.3).

Concomitant medication

All concomitant medication (incl. vitamins, herbal preparation and other "over-the-counter" drugs) used by the subject within 28 days of treatment start must be recorded in the CRF.

5.2.1 Telphone contacts by study nurse

The patient is asked about AEs and whether he or she is keeping the headache diary and whether there are problems with keeping it. The patient is also asked about ability to make forehead wrinkles.

5.2.2 Treatment visit

The headache diary is reviewed, AEs are registered, and a pregnancy test performed in WOCBP (as defined in 3.3). Vital signs (BP and pulse) are measured. If the patient is still eligible (inclusion and exclusion criteria, negative pregnancy test in fertile women), the patient can receive the treatment. Duration of the treatment procedure and bleeding , if any, in connection with the procedure is registered by the doctor. Pain during the injection procedure is indicated on VAS scale by patient just after injections. The headache diaries are collected from the patient

5.2.3 End of Study Visit

The headache diary is reviewed, and AEs are registered. Vital signs (BP and pulse) are measured, and all headache diaries are collected from the patient. The patient is also asked about ability to make forehead wrinkles.

5.2.4 Withdrawal Visit

Describe the sequence of procedures to be performed (by visit) as detailed in the time/event flowchart when the patient is withdrawn from the study before completing the study.

The headache diary is reviewed, AEs are registered. Vital signs (BP and pulse) are measured. The patient is also asked about ability to make forehead wrinkles.

5.2.5 After End of Treatment (Follow-up)

No follow-up is planned.

5.3 Criteria for Patient Discontinuation

Patients may be discontinued from study treatment and assessments at any time. Since the treatment is given only once and there is no antidote to the treatment, there is no reason to withdraw the patient from the study for safety reasons after the treatment.

Before treatment is given, specific reasons for discontinuing a patient for this study are:

- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment.
- Safety reason as judged by the Principal Investigator
- Major protocol deviation
- Incorrect enrolment ie, the patient does not meet the required inclusion/exclusion criteria for the study
- Patient lost to follow-up
- A female patient becoming pregnant
- Deterioration in the patients' condition which in the opinion of the Principal Investigator warrants study medication discontinuation (to be records as an AE or under Investigator Discretion)
- Patient's non-compliance to study treatment and/or procedures

5.4 Procedures for Discontinuation

5.4.1 Patient Discontinuation

Patients who withdraw or are withdrawn from the study, will stop further treatment.

Patients who are withdrawn from study before they receive treatment will not be followed up.

In the withdrawal visit the reason for discontinuation shall be recorded. The investigator will to follow up any significant adverse events until the outcome either is recovered or resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, fatal or unknown.
All patients randomized will be included in the study population.
Patients who withdraw or are withdrawn from the study cannot be replaced.

5.4.2 Trial Discontinuation

The whole trial may be discontinued at the discretion of the PI or the sponsor in the event of any of the following:

- Occurrence of AEs unknown to date in respect of their nature, severity and duration
- Medical or ethical reasons affecting the continued performance of the trial
- Difficulties in the recruitment of patients

The sponsor and principal investigator(s) will inform all investigators, the relevant Competent Authorities and Ethics Committees of the termination of the trial along with the reasons for such action. If the study is terminated early on grounds of safety, the Competent Authorities and Ethics Committees will be informed within 15 days.

5.5 Laboratory Tests

Only pregnancy tests in the urine will be performed on the treatment day in WOCBP (Definition, see 3.3).

6 ASSESSMENTS

6.1 Assessment of Efficacy (secondary endpoint)

- Course of headache as recorded in the headache diary (Appendix 1) before and after injection (efficacy variables, derived from the guidelines (18) and allowing comparison with the PREEMPT studies). The baseline period is mainly compared with the weeks 5-8 after the injections (1-5 below).

  1) Change from baseline in frequency of moderate/severe headache days (main efficacy variable). Moderate-severe headache day defined as headache lasting $\geq$ 4 hours where pain becomes at least moderate in intensity.

  2) Change from baseline in headache days headache day defined as headache lasting $\geq$ 4 hours where pain intensity may be mild, moderate, or severe.

  3) Change from baseline in frequency of migraine headache days

  4) change from baseline in frequency of acute headache pain medication intakes (all categories)

  5) Change from baseline in frequency of triptan intake

  6) Change from baseline in frequency of moderate/severe headache days week 1-12 after injection

6.2 Secondary Endpoints

- Duration of injection procedure (minutes) (See Appendix 4)

- Cosmetic effects (on forehead wrinkles).
  Patients will be asked at before each consultation to look in the mirror to detect differences in ability to make forehead wrinkles (no, mild, moderate, marked difference, full paralysis).

6.3 Safety and Tolerability Assessments (primary endpoint)

Safety will be monitored by the assessments described below as well as the collection of AEs at every visit. Significant findings that are present prior to the signing of informed consent must be included in the relevant medical history/ current medical condition page of the CRF. For details on AE collection and reporting, See Appendix 1 (Headache diary), section 1.5 (Primary endpoint), section 7, and Flow chart in 5.1).

AEs will be recorded in the diary (see Appendix 1) by the patient and reviewed during the scheduled visits. At each scheduled or unscheduled contact (visit or telephone), patients will be asked an open question about any medical problems that have occurred since the last contact, and these will also be recorded in the CRF. Patients can contact the doctor or study nurse throughout the study. Symptoms or signs that are clearly related to migraine will not be recorded.
Right after the injection the doctor will fill out a form about bleeding and other problems, and the patient will indicate on a VAS scale the level of pain of the procedure (See Appendix 4).

6.4 Other Assessments

None

7 SAFETY MONITORING AND REPORTING

Each patient will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.

The methods for collection of safety data are described below.

7.1 Definitions

7.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The term AE is used to include both serious and non-serious AEs.

Symptoms or signs that are clearly related to migraine will not be recorded. This includes typical migraine headache with concomitant nausea, vomiting, phono- or photophobia.

7.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- Results in death

- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Medical and scientific judgment is to be exercised in deciding on the seriousness of a case. Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the listed outcomes in the definitions above. In such situations, or in doubtful cases, the case should be considered as serious. Hospitalization for administrative reason (for observation or social reasons) is allowed at the investigator's discretion and will not qualify as serious unless there is an associated adverse event warranting hospitalization.

A pre-planned hospitalization admission (ie, elective or scheduled surgery arranged prior to the start of treatment) for pre-existing condition is not considered to be a serious adverse event.

7.1.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

This is a SAE (see section 8.1.2) that is unexpected as defined in section 8.2 and possibly related to the investigational medicinal product(s).

7.2 Expected Adverse Events

Weakness and stiffness of muscles in the area of injection (forehead, scalp), eyelid ptosis, pain and skin reaction at injection site.

7.3 Time Period for Reporting AE and SAE

For each patient the standard time period for collecting and recording AE and SAEs will begin at first injection on the treatment day and will continue for at least 12 weeks (84 days) following the injections for each patient.

During the course of the study all AEs and SAEs will be proactively followed up for each patient; events will be followed up to resolution, unless the event is considered by the investigator to be unlikely to resolve due to the underlying disease. Every effort will be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

7.4 Recording of Adverse Events

If the patient has experienced adverse event(s), the following information will be recorded in the CRF:

- The nature of the event(s) will be described by the investigator in precise standard medical terminology (i.e. not necessarily the exact words used by the patient).
- The duration of the event will be described in terms of event onset date and event ended data.
- The intensity of the adverse event.
- The Causal relationship of the event to the study medication will be assessed as one of the following:

Unrelated:

There is not a temporal relationship to investigational product administration (too early, or late, or investigational product not taken), or there is a reasonable causal relationship between non-investigational product, concurrent disease, or circumstance and the AE.

Unlikely:

There is a temporal relationship to investigational product administration, but there is not a reasonable causal relationship between the investigational product and the AE.

Possible:

There is reasonable causal relationship between the investigational product and the AE. Dechallenge information is lacking or unclear.

Probable:

There is a reasonable causal relationship between the investigational product and the AE. The event responds to dechallenge. Rechallenge is not required.

Definite:

There is a reasonable causal relationship between the investigational product and the AE.

- Action taken
- The outcome of the adverse event – whether the event is resolved or still ongoing.

7.5 Reporting Procedure

7.5.1 AEs and SAEs

All adverse events and serious adverse events that should be reported as defined in section 8.1.1 will be recorded in the patient's CRF.

SAEs will be reported within 24 hours after the site has gained knowledge of the SAE. Every SAE will be documented by the investigator on the SAE pages (to be found in <the investigator site file or as part of the CRF>). The Serious Adverse Event Report Form will be completed, signed and sent to Drug company (Allergan). The initial report shall promptly be followed by detailed, written reports if necessary. The initial and follow-up reports shall identify the trial subjects by unique code numbers assigned to the latter.

The sponsor keeps detailed records of all SAEs reported by the investigators and performs an evaluation with respect to causality and expectedness. Based on, among other, SAE reports the sponsor will evaluate whether the risk/benefit ratio associated with study is changed.

7.5.2 SUSARs

SUSARs will be reported to the Competent Authority and Ethics Committee according to national regulation. The following timelines should be followed:

The sponsor will ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the Competent Authority (In Norway: Ethical committee in Trondheim and to the medicinal authorities (In Norway: Statens Legemiddelverk). In Scottsdale, they will be reported to the Mayo Clinic Institutional Review Board. In any case they will be reported no later than seven (7) days after knowledge by the sponsor of such a case, and relevant follow-up information will subsequently communicated within an additional eight (8) days.

All other suspected serious unexpected adverse reactions will be reported to the Competent Authority concerned and to the Ethics Committee concerned as soon as possible but within a maximum of fifteen (15) days of first knowledge by the sponsor.

SUSARs will be reported using the CIOMS form (Appendix 5).

7.5.3 Annual Safety Report

Once a year throughout the clinical trial, the sponsor will provide the Competent Authority (In Norway: Statens legemiddelverk) with an annual safety report. The format will comply with national requirements.

7.5.4 Clinical Study Report

The adverse events and serious adverse events occurring during the study will be discussed in the safety evaluation part of the Clinical Study Report.

7.6 Procedures in Case of Emergency

In cases of emergency, the patients will be referred to the nearest relevant hospital department.

7.7 Data Monitoring Committee (DMC) (If applicable)

A clinical study monitor will be assigned, and will visit the investigator on a regular basis according to the monitoring plan. Such plan specific to this study is held separately to the protocol, and it will outline the level of monitoring to be performed for the trial and how this will be carried out. The

level of monitoring is based on the phase of the trial and any perceived risks identified by the risk assessment. Monitoring visits will commence after the Sponsor approves the plan.

8 DATA MANAGEMENT AND MONITORING

8.1 Case Report Forms

The CRF for this study will be designed by Gøril Gravdahl, study nurse, Norwegian Advisory Unit on Headaches, St. Olavs Hospital, Trondheim, Norway.

The designated investigator staff will enter the data required by the protocol into the Case report forms (CRF). The Investigator is responsible for assuring that data entered into the CRF is complete, accurate, and that entry is performed in a timely manner. The signature of the investigator will attest the accuracy of the data on each CRF. If any assessments are omitted, the reason for such omissions will be noted on the CRFs. Corrections, with the reason for the corrections will also be recorded.

The data will be entered into a database. The system used in this study is SPSS (Statistical Package for the Social Sciences). The setup of the database system will be performed by Gøril Gravdahl, study nurse, Norwegian Advisoryu Unit on Headaches, St. Olavs Hospital, Trondheim, Norway.

After database lock, the investigator will receive a digital copy of the subject data for archiving at the investigational site.

8.2 Source Data

Source data are all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

The medical records for each patient will contain information which is important for the patient's safety and continued care, and to fulfill the requirement that critical study data should be verifiable.

To achieve this, the medical records of each patient will clearly describe at least:

- That the patient is participating in the study, e.g. by including the enrollment number and the study code or other study identification;
- Date when Informed Consent was obtained from the patient and statement that patient received a copy of the signed and dated Informed Consent;
- Results of all assessments confirming a patient's eligibility for the study;
- Diseases (past and current; both the disease studied and others, as relevant);
- Surgical history, as relevant;
- Treatments withdrawn/withheld due to participation in the study;
- Results of assessments performed during the study;
- Treatments given, changes in treatments during the study and the time points for the changes;

- Visits to the clinic / telephone contacts during the study, including those for study purposes only;
- Non-Serious Adverse Events and Serious Adverse Events (if any) including causality assessments;
- Date of, and reason for, discontinuation from study treatment;
- Date of, and reason for, withdrawal from study;
- Date of death and cause of death, if available;
- Additional information according to local regulations and practice.

8.3 Study Monitoring

The investigator will be visited on a regular basis by the Clinical Study Monitor, who will check the following:

- Informed consent process
- Reporting of adverse events and all other safety data
- Adherence to protocol
- Maintenance of required regulatory documents
- Study Supply accountability
- Facilities and equipments (example: laboratory, pharmacy, ECG machine, etc...) if applicable

- Data completion on the CRFs including source data verification (SDV).

The monitor will review the relevant CRFs for accuracy and completeness and will ask the site staff to adjust any discrepancies as required.

Sponsor's representatives (e.g. monitors, auditors) and/or competent authorities will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study will be required.

8.4 Confidentiality

The investigator will arrange for the secure retention of the patient identification and the code list. Patient files shall be kept for the maximum period of time permitted by each hospital. The study documentation (CRFs, Site File etc) shall be retained and stored during the study and for 15 years after study closure. All information concerning the study will be stored in a safe place inaccessible to unauthorized personnel.

8.5 Database management

Data management will be performed by the (Gøril Gravdahl, nurse). The Data management procedures will be performed in accordance with the department's SOPs and ICH guidelines. The data management process will be described in the study specific data handling plan and the study specific data handling report after database closure.

Data entered into the database will be validated as defined in the data validation plan. Validation includes, but is not limited to, validity checks (e.g. range checks), consistency checks and customised checks (logical checks between variables to ensure that study data are accurately reported) for data captured in the database and external data (e.g. laboratory data).

Data management personnel will perform both manual CRF review and review of additional electronic edit checks to ensure that the data are complete, consistent and reasonable. The electronic edit checks will run continually throughout the course of the study and the issues will be reviewed manually online to determine what action needs to be taken.

Manual queries may be written by clinical data management or study monitor. Queries will be sent to the investigator for resolving. All updates to queried data will be made by clinical data management only and all modifications to the database will be recorded in an audit trail.

Adverse events and medical history will be coded from the verbatim description (Investigator term). Prior and concomitant medications and therapies will be coded according to the ATC code.

Once the database has been completed and locked, the Sponsor will authorise database lock and all electronic data will be sent to the designated statistician for analysis. Subsequent changes to the database will then be made only by written agreement.

The data will be stored in a dedicated and secured area at St. Olavs hospital, Trondheim, Norway. Data will be stored in a de-identified manner, where each study participant is recognisable by his/her unique trial subject number. The data will be stored until 31.12.2020.

9 STATISTICAL METHODS AND DATA ANALYSIS

9.1 Determination of Sample Size

This is an exploratory pilot study, with the main purpose to determine safety and tolerability of a new procedure. Hence, it is not possible to do a formal power calculation.

9.2 Randomization

Not relevant

9.3 Population for Analysis

The following populations will be considered for the analyses:

- Per-protocol population (PP): Includes all subjects who have received the injections and filled in the headache diary during weeks 5 to 8 after the injections.
- Safety population: Includes all subjects who have received the injections. Subjects who withdraw from the study will be included in the safety analysis. A list of withdrawn subjects, preferably with the reasons for withdrawal, will be made.

Since this is a study primarily concerned with safety and tolerability the primary analysis will be performed on the safety population. Effect evaluations will be performed on the per-protocol population.

9.4 Planned analyses

The main statistical analysis is planned when

- The planned number of patients have been included
- All included patients have either finalized their last assessment or has/is withdrawn according to protocol procedures

- All data have been entered, verified and validated according to the data management plan

Prior to the main statistical analysis, the data base will be locked for further entering or altering of data. A separate statistical analysis plan (SAP) will provide further details on the planned statistical analyses. The SAP will be finalized, signed and dated prior to database lock.

Deviation from the original statistical plan will be described and justified in the Clinical Study Report. Amendments to plan can be done until day of DB lock.

9.5 Statistical Analysis

The main result of the study is a tabulation of the different types of AEs and the proportion (± 95% confidence intervals) of treated patients with each type of AE after the injections, as well as time to resolution of the AE (or whether it is still ongoing at the end of the study). The same table will include the proportion with reduced ability to make forehead wrinkles, and also responder rates (≥ 50 % reduction). For these variables, no comparisons can be made.

The duration of the injection procedure (mean, range) will be given.

As to the main efficacy variable (of moderat/severe headache days), change from baseline to week 5-8 after the injection in the frequency of the event will be evaluated using paired t-test, or Wilcoxon signed rank test if the variable has a non-normal distribution. Similar analysis will be used for the other variables measuring change from baseline. $P<0.05$ (2-sided) is considered statistically significant.

10 STUDY MANAGEMENT

10.1 Investigator Delegation Procedure

The principal investigator is responsible for making and updating a "delegation of tasks" listing all the involved co-workers and their role in the project. He will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

10.2 Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations.
All significant protocol deviations will be recorded and reported in the Clinical Study Report (CSR).

10.3 Study Amendments

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) will be notified to and approved by the Competent Authority and the Ethics Committee according to EU and national regulations.

10.4 Audit and Inspections

Authorized representatives of a Competent Authority and Ethics Committee may visit the centre to perform inspections, including source data verification. Likewise the representatives from sponsor may visit the center to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and

data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (ICH GCP), and any applicable regulatory requirements. The principal investigator will ensure that the inspectors and auditors will be provided with access to source data/documents.

11 ETHICAL AND REGULATORY REQUIREMENTS

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements. Registration of patient data will be carried out in accordance with national personal data laws.

11.1 Ethics Committee Approval

The study protocol, including the patient information and informed consent form to be used, must be approved by the regional ethics committee before enrolment of any patients into the study.

The investigator is responsible for informing the ethics committee of any serious and unexpected adverse events and/or major amendments to the protocol as per national requirements.

11.2 Other Regulatory Approvals

The protocol will be submitted and approved by the applicable competent authorities before commencement of the study.

The protocol will also be registered in www.clinicaltrials.gov before inclusion of the first patient.

11.3 Informed Consent Procedure

The investigator is responsible for giving the patients full and adequate verbal and written information about the nature, purpose, possible risk and benefit of the study. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever she/he wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered in the study. This will be done in accordance with the national and local regulatory requirements. The investigator is responsible for obtaining signed informed consent.

A copy of the patient information and consent will be given to the patients. The signed and dated patient consent forms will be filed in the Investigator Site File.

11.4 Subject Identification

The investigator is responsible for keeping a list of all patients (who have received study treatment or undergone any study specific procedure) including patient's date of birth and personal number, full names and last known addresses.

The patients will be identified in the CRFs by patient number and initials.

12 TRIAL SPONSORSHIP AND FINANCING

The study is financed through the regular funds of the participating institutions.

13 TRIAL INSURANCE

Patients in Norway are insured through the Norwegian Drug Liability Insurance ("Legemiddelansvarsforsikringen") (See Appendix 6).

14 PUBLICATION POLICY

Upon study completion and finalization of the study report the results of this study will either be submitted for publication in an international scientific journal.

The results of this study will also be submitted to the Competent Authority and the Ethics Committee according to EU and national regulations.

All personnel who have contributed significantly with the planning and performance of the study (Vancouver convention 1988) may be included in the list of authors.

15 REFERENCES

16 LIST OF APPENDICES

1 Headache diary

2 Patient information and informed consent forms

3 Drug accountability form

4 Patient's and doctor's evaluation of the injection procedure

5 CIOMS form

6 Norwegian drug liability insurance

APPENDIX 1: HEADACHE DIARY

HEADACHE DIARY **Month:....., Year:.....**(See numeric codes and explanation at the bottom of the page) **NAME:**_____

USE THE BACK OF SHEET FOR REGISTRATION OF OTHER HEATH FACTORS

Date	Duration of headache (hours)	Headache intensity[1]	Functional ability[2]	Nausea[3]	Vomiting[3]	Sensitivity to light[3]	Sensitivity to sounds[3]	Medication[4]	Dose[5]	Medication[4]	Dose[5]	Medication[4]	Dose[5]	Did you have a migraine attack?[6]	Absence from work?[7]
1															
2															
3															
4															
5															
6															
7															
8															
9															
10															
11															
12															
13															
14															
15															

Headache intensity at maximum[1]
0=None
1=Mild
2=Moderate
3=Severe

Functional ability at maximum headache[2]
0=Normal
1=Reduced
2=Unable to function, bed rest not needed
3=bed rest required

Nausea, vomiting, sensitivity to light/sound[3]
0=No
1=Yes, a little
2= Yes, a lot

Medication[4]

Symptomatic medication (not preventive) against this attack and its additional symptoms

Dose[5]

number of tablets, injections nasal sprays and suppositories

Did you have a migraine attack?[6]
0=No
1=Yes
2=I don't know

Absence from work?[7]
0=No
1=Yes
2=Not applicable

INFORMATION ABOUT OTHER HEALTH FACTORS THAN HEADACHE

Date	Health problem	Treatment

APPENDIX 4: PATIENTS' AND DOCTORS' EVALUATION OF THE INJECTION PROCEDURE

Doctor's evaluation of the injection procedure

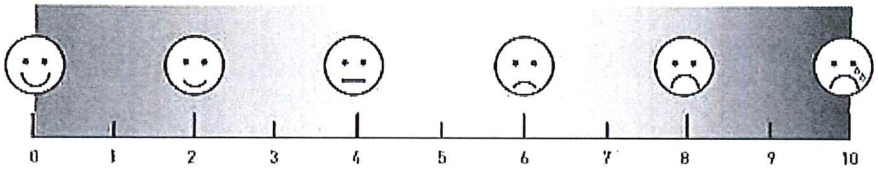
Duration of the procedure (minutes, from first till last injection):

Hemorrhages:

- No
- Mild
- Moderate
- Marked

Visual analogue scale for evaluating pain in conjunction with the injection procedure

On a scale from 0 (no pain) to 10 (worst imaginable pain), how would you rate the pain you felt in connection with the injections you just got. Make a mark on the scale below!



APPENDIX 3 DRUG ACCOUNTABILITY FORM

LEGEMIDDELREGNSKAP / *DRUG ACCOUNTABILITY FORM*

PROTOKOLL NUMMER *PROTOCOL NUMBER*		**STUDIESTED/ SENTER NR** *SITE/CENTER NO*	
LOKAL UTPRØVER *INVESTIGATOR AT SITE*		**PRODUSENT** *MANUFACTURER*	
TITTEL STUDIE *PROTOCOL TITLE*		**OPPBEVARING** *STORAGE CONDITIONS*	Temperatur fra oC til oC, beskyttet mot lys *Temperature range oC, protected from light*
STUDIEMEDISIN *STUDY MEDICATION*	Navn, pakningsstørrelse, konsentrasjon / styrke *Name, vial size, concentration / strength*	**LAGERPLASS** *STORAGE LOCATION*	

MOTTAK / *RECEIVED*					**UTLEVERING** / *DISPENSED*					**RETUR** / *RETURNED*			**DESTRUKSJON/ RETUR** *DESTRUCTION / RETURN*	**KOMMENTAR** *COMMENTS*
Medisin nummer *Medication ID*	Batch Utl.dato/ *Exp date*	Antall *Number*	Dato *Date*	Sign mottatt/ *received*	Pas nr./ initialer *Patient nr/ initials*	Antall *Number*	Dato *Date*	Sign utlevert *dispensed*	Lager-beholdning *Balance*	Antall *Number*	Dato *Date*	Sign	Dato/*Date* Sign	