# Follow the sutures. A new procedure for injection of Botulinum Toxin for Chronic Migraine.

## Statistical Analysis Plan

Version 1.0

# 1. Administrative information

| | |
|---|---|
| Sponsor name | St. Olavs Hospital |
| Sponsor address | Nevroklinikken, 7006 Trondheim, Norway |
| Unique protocol ID (Ethics approval) | 2017/1490 |
| Secondary IDs ( EUDRACT) | 2017/002516-13 |
| ClinicalTrials.gov | NCT03543254 |
| Trial title | Follow the sutures. A new procedure for injection of Botulinum Toxin for Chronic Migraine. |

SAP and protocol version

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|---|---|
| SAP version and date | This SAP is version 1, dated January 8, 2024 |
| Protocol version | This document was written based on information contained in the study protocol version 1.0, March 20, 2018 |

SAP revision history

| Protocol version | SAP version | Section number changed | Description and reason for change | Date changed |
|---|---|---|---|---|
| | 1.0 | | First edition of SAP | |

## 2. Signature page

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Signature

Date (08/01/2024)

## 3. Abbreviations

| | |
|---|---|
| PREEMT studies | ClinicalTrials.gov identifiers NCT00156910, NCT00168428 |

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## 4. Introduction

### 4.1 Background and rationale

The preclinical data suggest that a "follow-the-suture" approach to injections of onabotulinumtotoxin-A in patients with chronic migraine could represent an effective and less invasive and costly injection strategy than the currently employed pooled analysis of two large studies (PREEMPT-1 and 2) injection paradigm. The aim of the present pilot study was to develop a follow-the-suture injection paradigm and evaluate its feasibility, tolerability, and acceptability among patients with chronic migraine in an open-label pilot study

### 4.2 Trial objectives

#### 4.2.1 Primary objective

The primary objective was to develop a follow-the-suture injection paradigm

#### 4.2.2 Secondary objectives

Secondary objectives were to evaluate feasibility, tolerability, and acceptability among patients with chronic migraine in an open-label pilot study

### 4.3 Trial endpoints

#### 4.3.1 Primary endpoints

- The primary endpoint was number of adverse events recorded during the study.

#### 4.3.2 Secondary endpoints

- Compared to baseline, change in weeks 5–8 of: moderate/severe headache days (main efficacy variable), defined as headache lasting >4 h with at least moderate intense pain;
- Compared to baseline, change in weeks 5–8 of headache days, defined as a day with headache lasting >4 h with mild, moderate, or severe pain;

### 5.1 Trial design

An open-label pilot study

### 5.2 Randomization

No randomization was performed.

### 5.3 Sample size

Twenty patients with chronic migraine were included, all women.

### 5.4 Statistical framework

#### 5.4.1 Hypothesis test

The null hypothesis is that there is no difference in of adverse events compared to previous employed pooled analysis of two large studies (PREEMT 1 and 2).

#### 5.4.2 Statistical interim analyses

No interim analysis was performed in this pilot study.

5.4.3 Timing of final analysis
Adverse events was collected during the 3-month follow-up. Headache at baseline was compared to weeks 5–8 of follow-up.

5.4.4 Endpoint assessments
*5.4.4.1 Headache diary*
Patients were then given instructions in completion of a paper headache diary, where they recorded pain intensity and duration, concomitant migraine symptoms (nausea, vomiting, phono- and photophobia), acute medication (type, number of doses) and work absence (yes/no/not relevant). In addition, they were asked to record any adverse events.

5.5 Blinding procedure
The study is open-labelled.

## 6. Statistical principles

### 6.1 Confidence intervals and p-values
Statistically significant change from baseline was tested with a paired t-test. $P < 0.05$ was considered significant.

6.2 Adherence, protocol deviations and protocol violations
6.2.1 Headache diary adherence
The participant will be separated into two groups, filled in a headache diary and not filled in a headache diary

6.2.2. Protocol violations
Only number with complete data will be presented for each variable. No participant had protocol violation.

6.3 Analysis populations
The 20 participants with written consent

## 7. Trial population

7.1 Screening data, eligibility, and recruitment
Only patients with signed written consent will be reported.

7.2 Withdrawal/Lost to follow-up
Non patients with withdrawal or lost to follow-up

7.3 Baseline patient characteristics

The gender distribution, mean age, and use of acute and preventive medication will be given.

8. Analysis

8.1 Analysis of the primary efficacy endpoint
The primary outcome is number of adverse events recorded during the study. This will be given in a Table divided by timing of follow-up (baseline period, week 1-4, week 5-8, and week 9-12.

8.1.1 Statistical methods
Number of participants with adverse events will be given in each study period without statistical comparison.

8.1.2 Missing data
No data will be discarded.

8.2 Analysis of the secondary endpoints
For the secondary efficacy variables, mean values with standard deviations for each 4-week period, change (in %) between baseline and each 4-week period, and the whole 12-week period after injection were calculated. In patients who had recorded more than 4 weeks in the baseline period, only the first 28 days were considered. In the protocol, the secondary efficacy endpoint was defined as the change in week 5–8

8.2.1 Missing data
Missing data for secondary outcomes will not be imputed in this study.

8.3 Subgroup analyses
No subgroup analyses will be performed

9. Safety Analyses

9.1 Adverse Events
All adverse events and other health issues are registered in the paper version of the headache diary.

9.2 Clinical Laboratory Parameters
Not applicable.

9.3 Vital Signs
Not applicable.

10. Statistical Software

All statistical analyses will be done using SPSS version 27 (IBM corp., Chicago, IL).