Title: An open label study to evaluate the efficacy and tolerability of erenumab in the management of persistent redness and flushing in rosacea

STOP ROS Study

Danish title: Et åbent eksplorativt studie med henblik på at vurdere effekt og tolerabilitet af erenumab i behandling af persisterende rødme og flushing i rosacea

EudraCT number 2019-003971-20

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The study will start May 2020. The last patient and last visit will be conducted no later than January 2022.

Date: 01 December 2019

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1. OBJECTIVES

1.1 Primary endpoint

1. Mean change in number of days with moderate, severe or extreme flushing (defined as a score of 4-10 on the Flushing Assessment Tool part II[1]) from Baseline to week 12.

1.2 Secondary endpoints

1. Mean change in Clinician's Erythema Assessment (CEA)[2] from baseline to week 4, 8 and 12.
2. Mean change in Dermatology Life Quality Index (DLQI)[3] from baseline to week 4, 8 and 12.
3. Proportion of patients with at least 50% reduction in number of days with moderate, severe or extreme flushing (defined as a score of 4-10 on the Flushing Assessment Tool part II) from baseline to week 4, 8 and 12.
4. Mean change in number of days with moderate, severe or extreme flushing (defined as a score of 4-10 on the Flushing Assessment Tool part II) from baseline to week 4 and 8.
5. Mean change in Hospital Anxiety and Depression Scale (HADS)[4] from baseline to week 4, 8 and 12.
6. Proportion of patients with Investigator's Global Assessment (IGA)[5] '0' or '1' with an at least 2-point reduction from baseline to week 4, 8 and 12.
7. Mean change in Inflammatory Lesion Count (ILC) from baseline to week 4, 8 and 12.

8. Proportion of patients with at least 50% reduction in number of days with Patient's Self-Assessment (PSA) >2 from baseline to week 4, 8 and 12.
9. Mean change Patient's Self-Assessment (PSA) from baseline to week 4, 8 and 12.
10. Mean change in Quick Inventory Depressive Symptomatology (QIDS)[6] from baseline to week 4, 8 and 12.
11. Mean change in Rosacea Area and Severity Index (RASI)* from baseline to week 4, 8 and 12.
12. Mean change in Rosacea Clinical Scorecard (RCS)[7] from baseline to week 4, 8 and 12.
13. Mean change in Rosacea-specific Quality-of-Life index (RosaQoL)[8] from baseline to week 4, 8 and 12.

* Developed by the RASI group at the department of dermatology, Gentofte, Denmark

1.3 Tolerability

1. To evaluate the tolerability of erenumab through assessment of adverse events at every visit from baseline to week 4, 8 and 12.

2. BACKGROUND AND RATIONALE

2.1 Disease

Rosacea

Rosacea is a chronic inflammatory skin disorder with a prevalence of 5.46%[9]. Rosacea symptoms include persistent facial erythema with episodes of flushing in relation to triggers;

sun/heat, alcohol and stress, facial burning or stinging, and the recurrence of centrofacial papules and pustules (acne-like lesions). Treatment options for rosacea are inadequate and social consequences often high due to the visible and stigmatizing symptoms. The pathophysiology of rosacea remains unknown; however, rosacea has been associated with neurogenic inflammation and the upregulation of e.g. calcitonin gene-related peptide (CGRP)[10,11].

Interestingly, recent studies show a strong co-occurrence of rosacea and the headache disorder migraine[12]. The reason for this remains unknown, but disease activity in migraine has also been coupled to upregulation of neuropeptides such as CGRP and it has been suggested that the pathophysiology in migraine and rosacea is shared[12,13]. While CGRP antibodies such as erenumab have proven beneficial in migraine, the effect in rosacea is unknown, but this may potentially represent a major breakthrough in the treatment of rosacea.

In a recent single-case study at the Danish headache center, a patient who has chronic migraine and cooccurring rosacea was treated with erenumab 140 mg once every month. Treatment had a beneficial effect not only on her migraine symptoms, but, as a side-effect, her rosacea also improved during the treatment. This may potentially represent a major breakthrough in the management of rosacea.

2.3 Erenumab

Erenumab is a fully humanized monoclonal immunoglobulin (IgG2) antibody which targets the CGRP receptor. Erenumab binds to the CGRP receptor complex with high affinity (Kd of 20 pM) which competitively and reversibly blocks the binding of the native ligand, CGRP[14,15]. Erenumab has been approved for prophylactic treatment of migraine in Denmark and exists as a

subcutaneous injection of 70 mg or 140 mg[16,17].

Pharmacodynamics. No association has been observed between serum concentrations of erenumab and changes in systolic or diastolic blood pressure in neither migraine patients nor healthy volunteers at the dose of 140mg[18].

Pharmacokinetics and metabolism. Mean T_{max} is 5.5 (4 – 21 days). The half-life in a typical 70 kg person with a standard dose of 70 mg is approximately 21 days with the estimated half-life at higher doses being closer to that of a typical IgG2 (~23 days)[18]. There are no significant differences in pharmacokinetic properties between migraine patients and healthy volunteers[18]. Erenumab has no significant hepatoxicity as it is not eliminated through hepatic, biliary, or renal routes[14]. It has a very low risk of drug-to-drug interactions[14].

The potential mechanisms of action of CGRP receptor antagonists involve components of the trigeminal-vascular system and include normalization of CGRP-induced vasodilation, reduction of CGRP-induced neurogenic inflammation, and inhibition of pain transmission at the trigeminal ganglion and trigeminal nucleus[19–21]. Many of these components associated with migraine pathophysiology are outside the blood-brain barrier, and thus a peripherally restricted CGRP receptor antagonist could be efficacious. More recently, a positron emission tomography (PET) study with telcagepant, a small molecule CGRP receptor antagonist, showed little central nervous system receptor occupancy at a clinically efficacious dose[22]. Therefore, it is hypothesized that erenumab, a CGRP receptor antibody, will selectively antagonize the CGRP

receptors for prolonged periods, preventing and/or reversing the activation of the trigeminal-vascular system, resulting in the prevention of migraine headaches. The preclinical toxicology data were generated in cynomolgus monkey as it was the only laboratory species in which erenumab had suitable binding and functional activity. There were no significant findings in the toxicology studies that would predict a risk to human subjects. The no-observed adverse effect level (NOAEL) was the maximum dose evaluated in the 6-month Good Laboratory Practice (GLP) toxicology study, 150 mg/kg subcutaneous (SC). There were no significant effects on electrocardiogram (ECG) parameters, blood pressure (BP) or respiration rate in the single dose cardiovascular study in cynomolgus monkeys.

As of January 2017, 3632 subjects have received at least one dose of erenumab.

2.3.1 Clinical Efficacy

Clinical safety of erenumab in subjects with episodic and chronic migraine is being evaluated in 4 placebo-controlled studies; 1 completed phase 2 study (study 20120295) and 3 ongoing phase 2b/3 studies (study 20120178, 20120296, and 20120297), whose placebo-controlled periods have been completed. The placebo-controlled phases in these studies were 12 weeks, except in the case of Study 20120296, which was 24 weeks. These studies reported positive results for the shared primary efficacy endpoints: achievement of ≥ 50% reduction in monthly migraine days (in all 4 studies) and change from baseline in monthly acute migraine-specific medication treatment days (Studies 20120295, 20120296, and 20120297); this was an exploratory endpoint in Study 20120178.

2.3.2 Clinical safety

An integrated analysis of erenumab safety was conducted using data from ongoing/completed phase 2 and 3 studies (Study 20120178, 20120297, 20120296, 20120295, and 20130255 [the open-label extension phase of study 20120295]). The integrated safety data set comprised 2537 subjects with migraine, representing 2310.3 study years (SY) of exposure. During the initial 12-week double-blind period erenumab demonstrated a similar safety profile to placebo across 4 placebo-controlled studies. The incidence of treatment-related adverse events was 49.0% in the placebo group, 47.3% in the 70-mg group, and 46.0% in the 140 mg group. The majority of adverse events were grade 1 and 2 in severity and did not lead to withdrawal of erenumab. Overall, adverse events were low across treatment groups, and all but 1 adverse event (nasopharyngitis) occurred at a frequency < 5% (in all treatment groups). The most frequent adverse event (≥ 2%) in the erenumab group was nausea (2.7% vs 1.7%), fatigue (2.3% vs. 1.7%), nasopharyngitis (6.0% vs. 7.3%), and upper respiratory tract infection (3.5% vs. 3.0%). The percentages of subjects reporting serious adverse events were low in the erenumab group (1.0 and 1.7% in the integrated safety data set in the erenumab group and placebo group, respectively), and were similar among the placebo and erenumab treatment groups, with most events reported in single subjects only. Similarly, withdrawal of erenumab due to adverse events was low (1% and 2% in the integrated safety data set in the All erenumab group and placebo group, respectively) and was similar across treatment groups. There were no notable dose-dependencies for the majority of adverse events, and the adverse event profile for erenumab 70 mg was similar to that of 140 mg.

The safety profile of erenumab in the 6-month double-blind period of Study 20120296 was similar consistent with the 12-week safety profile. Over the long-term pool, which includes

subjects exposed to erenumab through the open-label extension (OLE) phases of the phase 2 and 3 studies and in subjects exposed to erenumab ≥ 12 months, the safety profile remained consistent with the adverse event profile during the initial 12-week period.

There were 2 fatal adverse events reported in the program, both occurring during open-label treatment with erenumab. The investigators considered that these fatal events were not considered treatment-related and are therefore not considered to represent a treatment-related safety signal.

Overall, based on comprehensive review of safety, erenumab has demonstrated a safety profile similar to placebo, and no key risks that could materially alter the risk profile of erenumab have been identified to date.

Based on the above safety data in more than 3500 migraine patients, we consider using erenumab in this patient population to be safe. Furthermore, the drug has been approved for use in migraine patients by the U.S. Food and Drug Administration and the European Medicines Agency.

Conclusion. As erenumab is not eliminated in potentially harmful routes and the rates of adverse events are non-significant, we do not expect any significant side effects or discomfort. A potential risk is cardiovascular outcomes in patients with pre-existing myocardial infarction, cardiovascular accident, transient ischemic attack, unstable angina and poorly controlled hypertension, which is why these patients will be excluded from this study. Thus, we consider that there is very little risk associated with the use of erenumab for a proof-of-concept in rosacea in the present study.

2.3.3 Safety study procedures

Possible side effects of taking blood samples are: soreness, pain, bruising, bleeding and/or or infection at the blood sample injection site. Subjects may experience nausea and/or headache when taking blood samples.

ECG may occasionally cause skin irritation may occur in relation t the location of the electrodes.

2.4 Rationale

Management of rosacea is an area of a large unmet medical need, with existing therapies having shown no or poor efficacy. CGRP receptor antagonism could represent a novel approach to rosacea management. Erenumab is a human monoclonal antibody, with a PK profile consistent with slow rise in serum concentration and relatively long half-life. The PK profile of erenumab is suitable for rosacea therapy. The present study is an open label exploratory study intended to assess the tolerability and efficacy of erenumab in reducing episodes of rosacea exacerbations and in improving general rosacea symptoms. This single-center open-label trial is undertaken to determine whether erenumab meets a basic level of efficacy in rosacea patients before conducting a larger multi-center placebo-controlled trial.

The current study was designed in a mix between the guidelines for rosacea diagnosis and treatment, and the current controlled trials for rosacea treatment, as the clinical guidelines for management of rosacea are not very satisfying. In the current study, the primary endpoint is to evaluate the mean change in days with moderate, severe or extreme flushing assessed by item 2 in FAST from baseline to week 12. Secondary endpoints include CEA, DLQI, HADS, IGA, ILC, PSA, QIDS, RASI, RCS and RosaQOL.

2.4.1 Rationale for erenumab doses

Erenumab 140 mg will be evaluated in the present study. Subjects will receive erenumab 140 mg subcutaneously for 12 weeks. Results from the Phase 2 study (Study 20120178) in subjects with episodic migraine demonstrated that the 70-mg dose resulted in statistically significant and clinically meaningful reductions in monthly migraine days at week 12 compared with placebo (70 mg: -3.40 vs Placebo: -2.28; Difference: -1.12; p = 0.02). In the chronic migraine study (Study 20120295), 70 and 140 mg erenumab were evaluated and showed that both 70 mg and 140 mg reduced the number of monthly migraine days with a safety profile similar to placebo[23], but in patients who have failed previous therapeutic drugs, which is the clinical case for rosacea patients, 140 mg gave a greater clinical benefit than 70 mg. Therefore, 140 mg is expected to be efficacious in this study.

2.4.2 Clinical Hypothesis

In subjects with rosacea, erenumab will reduce episodes of exacerbation and improve symptoms of rosacea.

3. EXPERIMENTAL PLAN

3.1 Study Design

An exploratory open-label study in patients with rosacea. The study will begin Primo 2019 and is expected to last one year. Approximately 30 subjects will be included and will receive erenumab 140 mg. The justifications for choosing an open-label design are the following:

1. There is currently no good approach for the pharmacologic management of rosacea.

Rosacea patients are known to be highly refractory to therapy, and patients have usually tried several drugs on/off for years with no or little benefit, e.g. doxycycline, tetracycline, isotretinoin and cutaneous metronidazole and ivermectin. None of these drugs are efficacious against episodes of flushing in rosacea. The first step is therefore to show whether erenumab is efficacious in reducing episodes of exacerbation and in improving rosacea symptoms in an otherwise treatment-refractory patient population.

2. The refractory nature of rosacea will lower the bias that could occur through placebo-effects and data will be compared with historical data from previous clinical trials in rosacea.
3. All endpoints are assessed after a 12-week treatment period, which is sufficient time to minimize placebo-effects.
4. Although relatively small, this exploratory open label study is needed to show whether there is an effect of erenumab in reducing episodes of exacerbation and in improving rosacea symptoms, and to provide an estimate of the effect before initiating larger multicenter double-blind placebo-controlled trials in this patient population.

3.2 Number of Subjects

The sample size justification is described in Section 10.5.

3.4 Replacement of Subjects

Subjects who are withdrawn or removed from the study will not be replaced.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

Each subject is expected to participate in the study for up to 24 weeks, which includes the following events:

• Screening

• 4-week run-in period

• 12-week open label treatment phase

• End of trial-visit (week 24) 12 weeks after last injection

3.5.2 End of Study

Study completion: When the last subject receives the final treatment or is discontinued from the study.

End of Trial: When the last subject completes the week 24 post-treatment evaluation or is discontinued from the study.

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates. Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 11).

4.1 Inclusion Criteria

Criteria to be met prior to enrollment in the 4-week run-in period:

- Erythematotelangiectatic rosacea with a minimum of 15 days in the run-in period of either:
    - PSA > 2 for a minimum 15 days, and/or
    - Moderate, severe or extreme flushing for a minimum of 15 days measured by the Flushing Assessment Tool (FAST)
- Men and women aged 18 – 65 years
- Minimum 12 months of rosacea prior to trial
- If patient has concurrent migraine, a daily headache diary must be filled out

4.2 Exclusion Criteria

- Systemic treatment for rosacea ended less than five half-lives or 28 days ago, whichever is longest
- Topical treatment for rosacea ended less than five half-lives or 28 days ago, whichever is longest
- Cardiovascular disease of any kind, including cerebrovascular disease
- Hypertension on the experimental day (systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg)
- Hypotension on the experimental day (systolic blood pressure < 90 mmHg and/or diastolic blood pressure < 50 mmHg)
- Ongoing psychiatric disease of any kind – unless it has been effectively treated with a stable treatment for at least 2 months.
- Anamnestic or clinical symptoms of any kind that are deemed relevant for study participation by the physician who examines the patient

- Pregnant or breastfeeding women, or women expecting to conceive during the study
- Women of childbearing potential who are unwilling to use an acceptable method of effective contraception during treatment through 16 weeks after the last dose of erenumab. Acceptable methods of effective birth control include not having intercourse (true abstinence, when this is in line with the preferred and usual lifestyle of the subject), hormonal birth control methods (pills, shots/injections, implants, or patches), intrauterine devices, surgical contraceptive methods (vasectomy with medical assessment of the surgical success of this procedure or bilateral tubal ligation), or two barrier methods (each partner must use one barrier method) with spermicide - males must use a condom with spermicide; females must choose either a diaphragm with spermicide, OR cervical cap with spermicide, OR contraceptive sponge with spermicide. Female subjects not of childbearing potential are defined as any female who: is post-menopausal by history, defined as:

  Age ≥ 55 years with cessation of menses for 12 or more months, OR

  Age < 55 years but no spontaneous menses for at least 2 years, OR

  Age < 55 years and spontaneous menses within the past 1 year, but currently amenorrhoeic (e.g. spontaneous or secondary to hysterectomy), AND with postmenopausal gonadotropin levels (luteinizing hormone and follicle-stimulating hormone levels > 40 IU/L) or postmenopausal estradiol levels (< 5 ng/dL) or according to the definition of "postmenopausal range" for the laboratory involved OR Underwent bilateral oophorectomy OR Underwent hysterectomy OR Underwent bilateral salpingectomy
- Known sensitivity to any component of erenumab

- Previously randomized into an erenumab study
- Member of investigational site staff or relative of the investigator
- Unlikely to be able to complete all protocol required study visits or procedures, and/or to comply with all required study procedures to the best of the subject's and investigator's knowledge

5. SUBJECT ENROLLMENT

Subjects will be recruited through flyers and posters at the Danish Headache Center, the department of Dermatology in Gentofte, specialized dermatology clinics, adverts in newspapers, adds in rosacea-specific groups on Facebook, adds in the daily press and via www.forsøgsperson.dk. Subjects may also be asked to participate when they come for their visit in the outpatient clinic at either The Danish Headache Center, the Department of Dermatology and Allergy in Gentofte, or in specialized dermatology clinics.

All subjects must personally sign and date the informed consent form before commencement of study-specific activities/procedures. Subjects who wish to participate will be given or sent the written patient information and the folder from the National Committee on health Research Projects: "Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt" (http://www.nvk.dk/~/media/NVK/Dokumenter/Forsoegspersoners-rettigheder-juli-2018.pdf?la=da), which they will be encouraged to read. Patients will be invited to an information-session and will be offered the opportunity to bring a friend and/or assessor. The information session will be held in a quiet room free from any disturbances with the investigator or a delegated medical doctor. After the written and oral information is given, the patient will be offered additional time (24 hours) to think about participating if needed. If the patient clearly

states that additional time to consider participation is not needed, the written consent will be signed. A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date in the subject's medical record and on the enrollment case report form (CRF).

The screening phase starts when the subject signs and dates the ICF and ends when the subject is included, or screen failed. The screening phase comprises a 4-week run-in period where baseline rosacea symptoms and intensity are recorded. Certain initial screening phase procedures may be repeated during the original initial screening phase.

(Note: Repeating procedures during the original initial screening phase is a part of screening and is not considered "re-screening.") These procedures include laboratory assessments with value(s) out of range due to sampling error or which could be within range with repeat sampling. All subjects who enter the screening phase for the study receive a unique subject identification number before any study procedures are performed. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is re-screened. A subject who is determined to be ineligible must be registered as a screen fail.

5.1 Re-screening

Investigators may re-screen a subject if the investigator is reasonably certain that reasons for screen failure will be resolved prior to or during a repeat screening attempt. Reasons to re-screen may include but are not limited to the following:

• Laboratory value(s) out of range due to sampling error or that might be within range after

medically appropriate supplementation. (Note: Before screen failing and then re-screening the subject, efforts should be made to repeat the laboratory assessment(s) during the original initial screening phase.);

• The subject does not comply with filling out the flushing assessment tool or the patient's self-assessment with more than 2 missing entries during the run-in period

• The subject has a medical condition that can be stabilized or resolved prior to the repeat screening attempt;

or

• Additional time is required following the subject's last dose of an excluded medication.

A subject must provide informed consent prior to the initiation of any re-screening procedures only if 30 or more days have elapsed since the date of the subject's initial informed consent. A subject may be screened up to 2 times (i.e., no more than 1 re-screen).

6. Treatment procedures

6.1 Erenumab

Erenumab will be packaged in prefilled syringes containing 1 mL of 140 mg/mL erenumab formulated with 15 mM sodium acetate, 8.5% (w/v) sucrose, 0.010% (w/v) polysorbate 80, at pH 5.2. Erenumab will be supplied by Novartis and will shipped to the Danish Headache Center with a temperature data logger. The delivery will be documented and signed by a secretary or lab technician and will proceed to be stored in a refrigerator with a temperature from set to 2-8°C. There will be written procedures and appropriate instructions for the personnel receiving

erenumab. The product can be kept at room temperature for 14 days (no more than max. 25°C), so there is no need to ship the drug in a cooled package.

6.2 Dosage, Administration, and Schedule

Erenumab 140 mg will be administered monthly by subcutaneous (SC) injections during the 12-week open label (i.e., at day 1 and weeks 4 and 8). The erenumab dose is fixed and will not be adjusted for individual subjects during the study. One SC injection is to be given for each erenumab administration. The anatomical sites for administration of erenumab are the upper arm, upper thigh, or abdomen. Please see the European Medicines Agency product information on erenumab[24].

Overdose with this product has not been reported. Only authorized investigational site study staff members are to administer erenumab. The quantity, start date, batch number and box number of erenumab are to be recorded on each subject's CRF.

6.3 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

The dosage of erenumab is fixed for all subjects and cannot be adjusted. Missed or delayed doses should be noted on the erenumab administration CRF, but no attempt should be made to administer any missed doses at the subject's next visit. At any time during the study, the investigator may discontinue erenumab administration for any subject who experiences a severe or life-threatening adverse event reported by the investigator to be related to erenumab. Refer to Section 9 for details regarding adverse event reporting. Subjects who permanently discontinue erenumab during the treatment phase are to continue to return for all other study procedures until

the end of the tolerability follow-up visit 12 weeks after the last dose of erenumab.

6.4 Concomitant Therapy

Throughout the study and while the subject is receiving erenumab, investigators may not prescribe any concomitant medications for rosacea, but they may prescribe treatments deemed necessary to provide adequate supportive care. For a subject who prematurely discontinues erenumab, concomitant therapy may be adjusted as needed.

Concomitant therapies are to be collected from the informed consent through the end of study. The therapy name, indication, dose, unit, frequency, start date, and stop date are to be recorded on each subject's CRF. No other rosacea-specific treatment is allowed throughout the study.

6.5 Medical Devices

Medical devices which are not considered test articles may be used in the conduct of the study as part of standard of care. These devices, such as alcohol prep pads, are commercially available and the investigator will be responsible for obtaining supplies of these devices.

6.6 Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of any product(s) or device(s) after it is released to the clinic. Any product complaint(s) associated with erenumab or non-investigational product(s) or device(s) will be reported.

7. STUDY PROCEDURES

Refer to the Schedule of Assessments (Table 1) for an outline of the procedures required at each study visit. Refer to the applicable supplemental manuals (e.g., laboratory, ECG) for detailed collection and handling procedures. Allowable windows for visits are the following:

• Each study visit during the 12 weeks has a window of ± 4 consecutive calendar days.

• The day 1 visit has a window of 0, +7 consecutive calendar days; the day 1 visit must occur 28 to 35 days after the week -4 visit date.

• All study visit target dates are to be calculated from the day 1 visit date.

• All study procedures for a given study visit are to be completed on the same day.

Investigators are responsible for ensuring that all study procedures are performed as specified in the protocol.

Study visits should be conducted without additional non-protocol therapies and subjects should be reminded about the investigational nature of the study drug.

7.1 Schedule of Assessments

Table 1. Schedule of Assessments- Study Visits

Procedures	Screening	Week -4	Day 1	Week 4	Week 8	Week 20
Study visit		**x**	**x**	**x**	**x**	**x**
Phone call	**x**					
Information and	**x**					

informed consent sent via email						
Demography	**x**					
Erenumab dose			**x**	**x**	**x**	
Medical and medication	**x**	**x**	**x**	**x**	**x**	**x**
Physical exam		**x**				**x**
Physical measurements		**x**	**x**	**x**	**x**	**x**
Vital signs		**x**	**x**	**x**	**x**	**x**
ECG		**x**	**x**			**x**
Pregnancy testing		**x**	**x**	**x**	**x**	**x**
Chemistry hematology		**x**				
Adverse events			**x**	**x**	**x**	**x**
CEA		**x**	**x**	**x**	**x**	**x**
DLQI		**x**	**x**	**x**	**x**	**x**
FAST		**x**	**x**	**x**	**x**	**x**
HADS		**x**				**x**
Headache Reporting		**x**	**x**	**x**	**x**	**x**
IGA		**x**	**x**	**x**	**x**	**x**
ILC		**x**	**x**	**x**	**x**	**x**

PSA		**x**	**x**	**x**	**x**	**x**
QIDS		**x**				**x**
RASI		**x**	**x**	**x**	**x**	**x**
RCS		**x**	**x**	**x**	**x**	**x**
RosaQOL		**x**	**x**	**x**	**x**	**x**
Standardized photography		**x**	**x**	**x**	**x**	**x**

CEA = Clinician's Erythema Assessment, DLQI = Dermatology Life Quality Index, FAST = Flushing Assessment Tool, HADS = Hospital Anxiety and Depression Scale, IGA = Investigator's Global Assessment, ILC = Inflammatory Lesion Count, PSA = Patient's Self-Assessment, QIDS = Quick Inventory of Depressive Symptomatology, RASI = Rosacea Area and Severity Index (still being developed), RCS = Rosacea Clinical Scorecard, RosaQOL = Rosacea-Specific Quality-of-Life.

Each visit during the study has a window of ± 4 consecutive calendar days. The day 1 visit has a window of 0, +7 consecutive calendar days; the day 1 visit must occur 28 to 35 days after the week -4 visit date. All study visit target dates are to be calculated from the day 1 visit date. All study procedures for a given study visit are to be completed on the same day.

7.2 General Study Procedures

7.2.1 Informed Consent

All subjects must personally sign and date the approved ICF before any study-specific procedures are performed.

7.2.2 Medical and Medication History

A review of medical and medication history will be performed at initial screening to confirm subject eligibility.

Targeted medical history is to be recorded in the Neurologic Medical History CRF and Cardiovascular Medical History CRF, and other medical history is to be recorded in the General Medical History CRF.

Source notes for subjects referred to the research site must include all of the above information.

7.2.3 Physical Examination

A complete physical examination (PE) per standard of care (including neurological exam) will be performed on all subjects. Any clinically significant anomalies noted during the initial screening phase are to be detailed in the Medical History CRF. Investigators are to check for any findings that would constitute study exclusion.

7.2.4 Physical Measurements

The following measurements are to be performed: height (week -4) and weight. Height and weight are to be measured without shoes. Body Mass Index (BMI) should be calculated using the following formula: BMI (kg/m2) = weight (kg)/[height (cm)/100]. All measurements are to be

recorded on the Physical Measurements CRF.

7.2.5 Vital Signs

The following measurements are to be performed: Systolic/diastolic blood pressure, heart rate, and body temperature. Blood pressure will be measured in the following manner:

• Subjects should be lying in a semi-recumbent position (partial semi-Fowler's position) or supine position quietly and comfortably for at least 5 minutes. The upper arm should be bare without constrictive clothing and supported at heart level.

• Caffeine, exercise, and smoking should be avoided for at least 30 minutes prior to measurement.

• An appropriately sized cuff (cuff bladder encircling at least 80 percent of the arm) should be used to ensure accuracy. At least two measurements (separated by at least 5 min) should be made and the average recorded. If there is a high value, it is acceptable to wait approximately 30 minutes before the next two blood pressure measurements are taken for the purpose of averaging and recording in the CRF.

• Blood pressure will initially be recorded in both of the subject's arms unless a concomitant condition favors the use of a particular arm. The arm with the higher systolic reading at initial screening should then be used for blood pressure determinations throughout the study.

• Neither the subject nor the observer (measurer) should talk during measurement.

The position selected for a subject (i.e., semi-recumbent or supine) should be the same that is used throughout the study and documented on the Vital Signs CRF.

The temperature location selected for a subject should be the same that is used throughout the

study and documented on the Vital Signs CRF.

All measurements are to be recorded on the Vital Signs CRF.

If abnormalities in vital signs are found and they are considered to be adverse events, they will be recorded on the adverse event summary CRF.

7.2.6 Pregnancy Testing for Women of Childbearing Potential

Female subjects of childbearing potential will have a urine pregnancy test at initial screening to confirm subject eligibility. All urine pregnancy testing will be performed by the local laboratory.

7.2.7 Electrocardiogram (ECG)

The subject must be in a supine position in a rested and calm state for at least 5 minutes before the ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position as possible. The ECG must include the following measurements: Heart Rate, QRS, QT, QTc, and PR intervals.

The central reader will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents.

It is the responsibility of the investigator to determine if the ECG tracings are consistent with a subject's safe participation in the study.

Any ECG abnormality noted by the central reader must be evaluated by the investigator to determine if the ECG finding is representative of an unstable or clinically significant medical condition.

Please refer to the central ECG reader manual for details.

7.2.8 Adverse Event Reporting

Adverse event information should be collected throughout the study and recorded at each study visit. Professor Messoud Ashina is both the sponsor and investigator in this study, so all adverse events will be reported from investigator to sponsor.

7.2.9 Laboratory Assessments

The local laboratory will be used for the following parameters:

Hemoglobin, white blood cell count, ALP, ALT and total bilirubin will be collected at week –4 visit for safety reasons. There is no need to monitor further lab test when treated with erenumab according to according to the summary of product characteristics. A total of 6 mL blood is expected to be drawn at this visit and after analysis no blood will from this sample will be stored.

7.2.10 Clinician's Erythema Assessment

The Clinician's Erythema Assessment (CEA)[2] (appendix 2) is short-form investigator-administered rating scale. The CEA is used to rate redness that is present at the time of rating. It is a 5-point investigator-completed rating scale using numerical analogue scale (0=clear to 4=severe). Investigator will complete the CEA monthly at each clinical visit.

7.2.11 Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) questionnaire is designed for use in adult patients with any skin problem. The DLQI is used to assess how much the patient's skin problem has

affected the patient's life within the previous week. It is a self-administered short 10-item patient-completed assessment using numerical analogue scale (0=not at all/not relevant to 3=very much). The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. "0-1 = no effect at all on patient's life", "2-5 = small effect on patient's life", "6-10 = moderate effect on patient's life", "11-20 = very large effect on patient's life", "21-30 = extremely large effect on patient's life"

The DLQI is used to assess any change in life quality and will be filled out at baseline and every 4 weeks during every clinical visit until week 12.

7.2.12 Flushing Assessment Tool

The Flushing Assessment Tool (FAST)[1] (appendix 1) developed to assess flushing symptoms and impact on patients. It was developed to patients receiving niacin therapy, but it may be used to assess the efficacy of other treatments. The FAST tool will be filled out daily to capture the flushing experience of patients on a daily basis. Specifically, the FAST tool captures the severity and troublesomeness of flushing overall and severity for each individual component of flushing (cutaneous warmth, redness, itching and tingling) and the impact of flushing on usual daily activities and sleep. FAST results in FAST score (mean standard deviation between 0 – 1) for each of the following parameters: mean flushing event severity, maximum flushing event severity, severity of flushing-related redness, severity of flushing-related warmth, severity of flushing-related tingling, severity of flushing-related itching, overall flushing troublesome score, overall flushing sleep troublesome score, overall flushing daily activities impact score.

7.2.13 Hospital Anxiety and Depression Scale

Hospital Anxiety and Depression Scale (HADS) is a 14-item self-reported questionnaire to evaluate the severity of depressive symptoms and symptoms of anxiety with patients rating symptoms from 0 to 3 where 0 is no symptoms. this results in a total score of 0 – 21 on either depression or anxiety where 0-7 = normal, 8 – 10 = borderline abnormal (borderline case), and 11-21 = abnormal (case).

7.2.14 Investigator Global Assessment

The Investigator Global Assessment (IGA)[5] (appendix 3) is a short-form physician/ investigator-administered rating scale. The IGA is used to rate severity of rosacea at the time of rating. It is a 5-point investigator-completed rating scale using numerical analogue scale (0=clear to 4=severe). Investigator will complete the IGA every 4 weeks during the clinical visit until week 12.

7.2.15 Inflammatory Lesion Count

The Inflammatory Lesion Count (ILC) is a physician/investigator assessment of number of inflammatory lesions (papules + pustules + nodules). ILC is used to evaluate the change in severity of papulopustular rosacea baseline to week 12 and will be assessed at every clinical visit.

7.2.16 Patient's Self-Assessment

Patient's Self-Assessment (PSA)[25] (appendix 2) is short-form self-administered rating scale. The PSA is used to rate redness that is present at the time of rating. It is a 5-point patient-

completed rating scale using numerical analogue scale (0=clear to 4=severe). Subjects will complete the PSA every day for the whole study period from week -4 to week 12.

7.2.17 Quick Inventory of Depressive Symptomatology

The Quick Inventory of Depressive Symptomatology (QIDS) is a self-reported 16-item screening tool containing questions about sleep, mood, appetite, weight, self-view and thoughts of death or suicide, interest, energy level and restlessness to evaluate whether the patient has symptoms of depression.

7.2.18 Rosacea Area and Severity Index

Rosacea Area and Severity Index (RASI) is a tool that is currently being validated by the RASI group at the department of Dermatology in Gentofte. It is designed to evaluate major manifestations of rosacea, including erythema, papules/pustules, telangiectasias and rhinophyma, which will be rated on a scale from 0 – 3 with 0 being no symptoms and 3 being severe symptoms. These manifestations of rosacea will also be assessed according to area and percentage of this area affected which will result in a score from 0 – 72 with 0 being no manifestations of rosacea and 72 being the most severe manifestations. RASI is being developed and validated against established objective and subjective markers in rosacea, to develop a collective index for measuring overall disease severity and monitoring changes during treatment.

7.2.19 Rosacea Clinical Scorecard

The Rosacea Clinical Scorecard (RCS) (appendix 4) is a scorecard used by the physician/investigator to assess primary and secondary features of rosacea. It is designed by the national rosacea society in the United States of America in order to assess all features of rosacea

according to the standard grading scale.

It includes the following primary features: flushing, non-transient erythema, papules and pustules, telangiectasia, and the following secondary features: burning or stinging, plaques, dry appearance, edema, location, phymatous changes, granulomatous changes. Features are assessed on a qualitative scale (absent, mild, moderate, severe) and results in a global assessment of rosacea subtype(s) and severity. RCS will be filled out at Baseline and every 4 weeks during every clinical visit until week 12.

7.2.20 Rosacea-Specific Quality of Life

The Rosacea-Specific Quality of Life (RosaQOL) (appendix 5) is a 21-item self-reported quality-of-life instrument developed specifically to evaluate life quality in rosacea patients. Questions are related to either symptoms or emotions related to rosacea manifestations or emotions and are rated on a 5-point scale ‘never, rarely, sometimes, often, always’.

7.2.21 Standardized photography

A standardized photography will be taken at baseline, day 1 and every four weeks (on visit at the clinic) during the whole study period.

Photographs will be used to evaluate the treatment response clinically every four weeks. Three doctors, JT, AE and NW will evaluate the photos and disagreements will be solved by discussion.

7.2.22 Headache Reporting

Questions on headache will be reported every day during the study period. Patients will be asked whether they experience headache during the past 24 hours. If they experienced headache during the past 24 hours, they will be asked to answer additional questions about their most severe headache during the past 24 hours to determine whether this headache fulfills criteria for migraine.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution. Subjects (or a legally acceptable representative) can decline to continue receiving erenumab and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from erenumab or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 1) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Table 1) and the level of follow-up that is agreed to by the subject (e.g. in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in

the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

8.2 Investigator or Sponsor Decision to Withdraw or Terminate

Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Subjects may be eligible for continued treatment with erenumab and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.1.

8.3 Reasons for Removal from Treatment, or Study

8.3.1 Reasons for Removal from Treatment

Reasons for removal from protocol-required erenumab or procedural assessments include any of the following:

• subject request

• safety concern (e.g., due to an adverse event, ineligibility determined, protocol deviation, non-compliance and pregnancy).

• death

• lost to follow-up

• decision by sponsor (other than subject request, safety concern, lost to follow-up)

8.3.2 Reasons for Removal from Study

Reasons for removal of a subject from the study are:

• decision by sponsor

• withdrawal of consent from study

• death

• lost to follow-up

9. TOLERABILITY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment.

The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record. The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-

existing medical condition (e.g., diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an adverse event. An adverse device effect is defined as any adverse event related to the use of a medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

The reference document used to assess adverse events is the Danish product information as this trial will only be conducted in Denmark (https://www.ema.europa.eu/documents/product-information/aimovig-epar-product-information_da.pdf)

9.1.2 Definition of Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

• fatal

• life threatening (places the subject at immediate risk of death)

• requires in-patient hospitalization or prolongation of existing hospitalization

• results in persistent or significant disability/incapacity

• congenital anomaly/birth defect

• other medically important serious event

An adverse event would meet the criterion of "requires hospitalization," if the event necessitated an admission to a health care facility (e.g, overnight stay). If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event." Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Reporting of Adverse Events

The investigator is responsible for ensuring that all adverse events and pregnancy reporting observed by the investigator or reported by the subject that occur after the first dose of investigational product through the end of the tolerability follow-up visit 12 weeks after the last dose of erenumab) are reported using the applicable CRF. The investigator is responsible for ensuring that all adverse events and pregnancy reporting observed by the investigator or reported by the subject that occur after signing of the informed consent through the end of the tolerability follow-up visit (12 weeks after the last dose of erenumab) are recorded in the subject's medical record. All deadly or life-threatening suspected unexpected serious adverse events (SUSARs)

will be reported to the Danish Medicines Agency (DMA) as fast as possible and within 7 days. Furthermore, within 8 days after reporting a related serious adverse event to the DMA, the DMA will receive a report of on the follow-up of the related serious adverse event by the sponsor/investigator. All other SUSARs will be reported within 15 days. After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for adverse events. However, if the investigator becomes aware of SUSARs after this protocol-required reporting period, the investigator will report the event to the DMA. The reference used to assess if a serious adverse event is expected or unexpected is the Danish product information as this trial will only be conducted in Denmark (https://www.ema.europa.eu/documents/product-information/aimovig-epar-product-information_da.pdf)

10. STATISTICAL CONSIDERATIONS

10.2 Study Endpoints and sample size

10.2.1 Primary endpoints

1. Mean change in number of days with moderate, severe or extreme flushing (defined as a score of 4-10 on the Flushing Assessment Tool part II) from Baseline to week 12.
2. Mean change in Dermatology Life Quality Index (DLQI)[3] from baseline to week 12.

10.2.2 Secondary endpoints

1. Mean change in number of days with Patient's Self-Assessment (PSA) > 2 from baseline to week 12 through weeks 4 and 8.
2. Mean change I Dermatology Life Quality Index (DLQI) from baseline to week 4 and 8.
3. Proportion of patients with at least 50% reduction in number of days with moderate, severe or extreme flushing (defined as a score of 4-10 on the Flushing Assessment Tool part II) from baseline to week 4, 8 and 12.
4. Proportion of patients with at least 50% reduction in number of days with Patient's Self-Assessment (PSA) >2 from baseline to week 4, 8 and 12.
5. Proportion of patients with Investigator's Global Assessment (IGA)[5] '0' or '1' with an at least 2-point reduction from baseline to week 4, 8 and 12.
6. Mean change in number of days with moderate, severe or extreme flushing (defined as a score of 4-10 on the Flushing Assessment Tool part II) from baseline to week 4 and 8.
7. Mean change in Rosacea-specific Quality-of-Life index (RosaQoL)[8] from baseline to week 4, 8 and 12.
8. Mean change in Hospital Anxiety and Depression Scale (HADS)[4] from baseline to week 4, 8 and 12.
9. Mean change in Quick Inventory Depressive Symptomatology (QIDS)[6] from baseline to week 4, 8 and 12.

10. Mean change in Rosacea Clinical Scorecard (RCS)[7] from baseline to week 4, 8 and 12.
11. Mean change in Clinician's Erythema Assessment (CEA)[2] from baseline to week 5, 8 and 12.
12. Mean change in Inflammatory Lesion Count (ILC) from baseline to week 4, 8 and 12.
13. Mean change in Rosacea Area and Severity Index (RASI)* from baseline to week 4, 8 and 12.

* Still being developed

10.3 Tolerability

1. To evaluate the tolerability of erenumab through assessment of adverse events at every visit from baseline to week 4, 8 and 12.

10.4 Sample Size Considerations

We wanted to detect at least a 3-day difference in monthly days with moderate to severe flushing from baseline to week 12. With 80% power at 5% significance level and a proposed standard deviation of 5 days, this renders a sample size of 24 patients which we have rounded up to 30 patients to account for variance.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

The written informed consent document is written in Danish. Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or erenumab is administered.

The investigator also is responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject.

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol proposed informed consent form, other written subject information, and

any proposed advertising material must be submitted to the independent ethics committee (IEC) for written approval. The investigator must submit and, where necessary, obtain approval from the IEC for all subsequent protocol amendments and changes to the informed consent document.

11.3 Subject confidentiality

The investigator must ensure that the subject's confidentiality is maintained.

• Subjects are to be identified by a unique subject identification number.

• On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

• In compliance with ICH GCP Guidelines, it is required that the investigator, sponsor and institution permit authorized representatives of the regulatory agency(s), and the IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Study Documentation and Archive

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Delegation of Authority Form. Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries may be considered source data if the CRF is the site of the original recording (i.e., there is no other written or electronic record of data).

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by applicable regulatory authorities.

Elements to include:

• Subject files containing completed CRFs, informed consent forms, subject identification list

• Study files containing the protocol with all amendments, and all correspondence to and from regulatory authorities.

• Study drug correspondence including Proof of Receipts (POR), Erenumab Accountability Record(s), Return of study drug for Destruction Form(s), Final study drug Reconciliation Statement, as applicable.

• Medical device (i.e., syringes) documentation, as applicable

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

Retention of study documents will be governed by the Clinical Trial Agreement.

12.2 Study Monitoring and Data Collection

The study will be conducted in accordance with the General Data Protection Regulation. The regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (e.g. CRFs and other pertinent data), provided that patient confidentiality is maintained.

The GCP clinical monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The clinical monitor may have access to subject medical records and other study-related records needed to verify the entries on the CRFs.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

12.3 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all

protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 1), the investigator can search publicly available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.4 Publication Policy

• Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3, and 4.

The results will be published in an international peer-reviewed scientific journal. Both positive, negative and inconclusive results will be published. The study will also be submitted to clinicaltrials.gov

• Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

• All persons designated as authors should qualify for authorship, and all those who qualify should be listed.

• Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

12.5 Compensation

Patients will be compensated for any reasonable expenses involved with the trial regarding transportation. Any arrangements for compensation to subjects for injury or illness that arises in the study will be subject to the Patient Compensation Association (Patienterstatningen).

12.6 Study Funding

The study is initiated by the investigator professor Messoud Ashina and sponsored by Novartis who will deliver the drug necessary for conducting the study. The market price for erenumab for one injection of 70 mg is 4.344,60 DKR. Thus, this amounts to a total market price of 782.028 DKR if 30 rosacea patients receive 140 mg three times.

12.7 Ethical considerations

The Declaration of the Helsinki Declaration of 2013. The participants will only be included after full written and oral information as well as written acceptance. The trial participants may withdraw from the investigation at any time without justification and it will not affect future treatment. The adverse reaction profile for erenumab is estimated to be well documented as previously described, and minor nuisances are expected in connection with ECG and blood sampling. Rosacea is a frequent and disabling disease where evidence-based treatment is not yet available and patients with the disease are often treatment-resistant. This open-label trial is performed to determine if erenumab shows a basic level of effect in patients with persistent erythema and flushing in rosacea, which is expected to form the basis for a future major multicenter placebo-controlled trial. It is our opinion that the expected disadvantages, discomfort and risks to the participants are proportionate to the significance of the expected results.

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Appendix 1 – Flushing Assessment Tool (FAST)

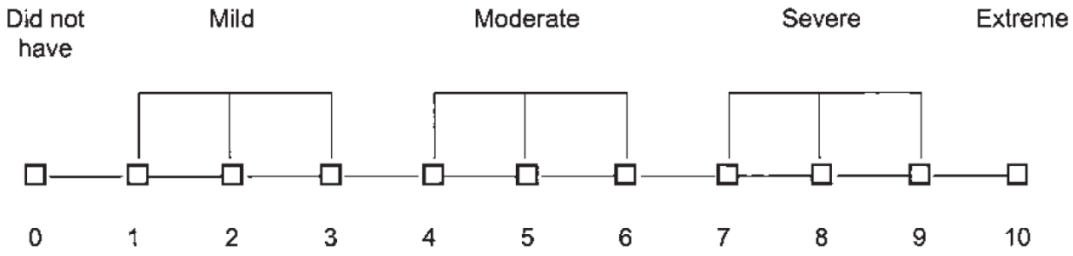
Will be handed out to patient to fill out daily during the whole study period.

Flushing symptoms questionnaire

For the following questions, please think about flushing symptoms (including redness, warmth, tinging or itching of your skin) you may have had during the past 24 hours.

1. During the past 24 hours, how many times did you have flushing symptoms (including redness, warmth, tingling or itching of your skin? (response options: did not have, 1, 2, 3 or more)

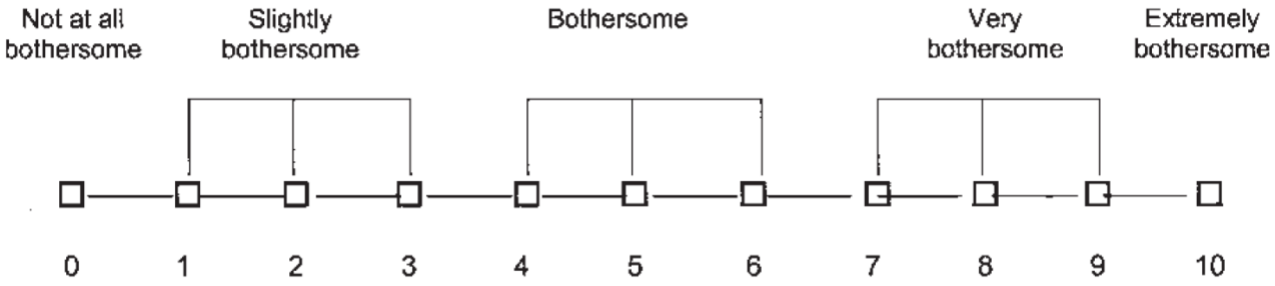
2. OVERALL during the past 24 hours, how would you rate your flushing symptoms (including redness, warmth, tingling or itching of your skin)?



3. During the past 24 hours, about how long did your longest flushing symptoms last (including redness, warmth, tingling or itching of your skin)? (response options: did not

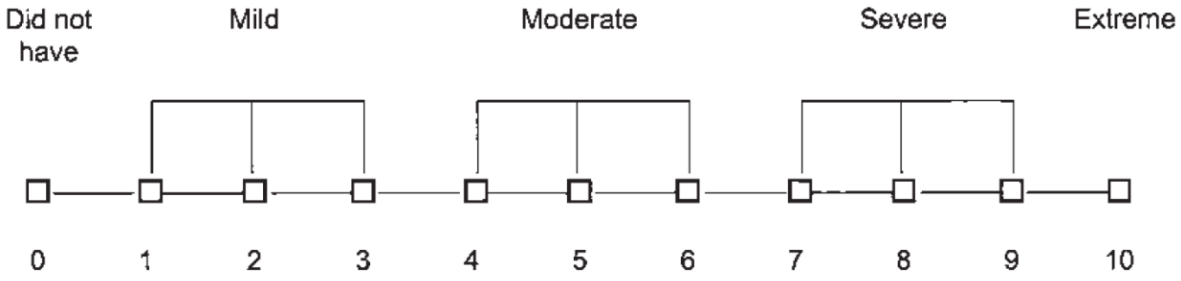
have, <5 minutes, 5 minutes to 2 hours in 5-minute increments. More than 2 hours. Don't know)

4. OVERALL during the past 24 hours, how BOTHERSOME were your flushing symptoms (including redness, warmth, tingling or itching of your skin)?

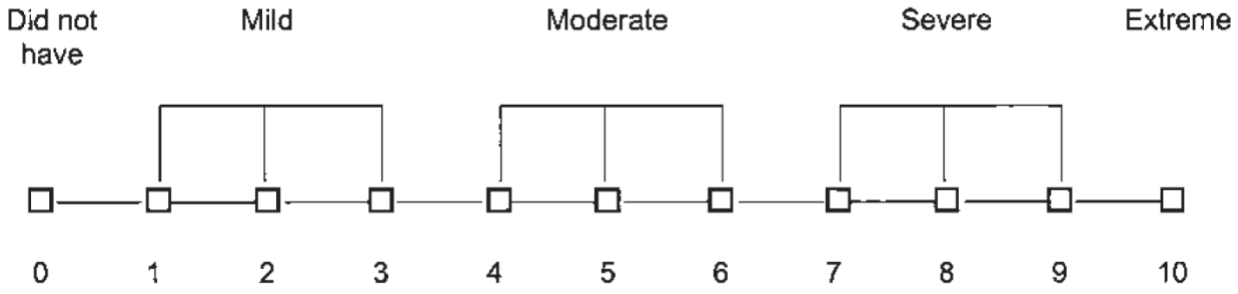


The next questions are about the SEPARATE flushing symptoms of redness, warmth, tingling, and itching of your skin.

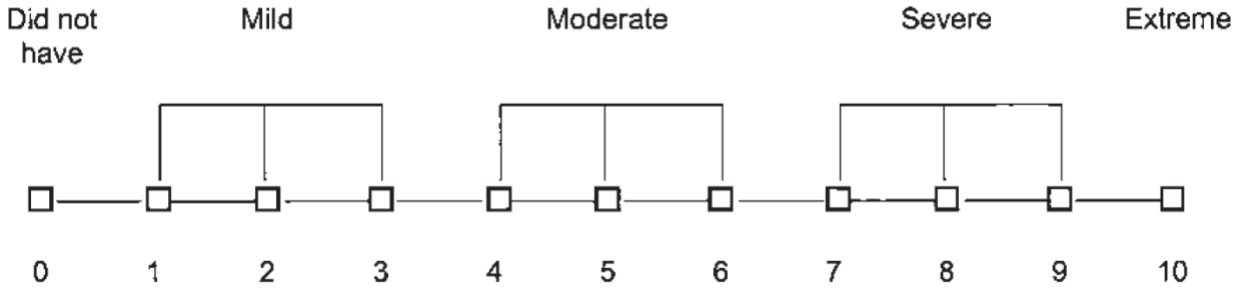
5. During the past 24 hours, how would you rate the flushing-related REDNESS of your skin?



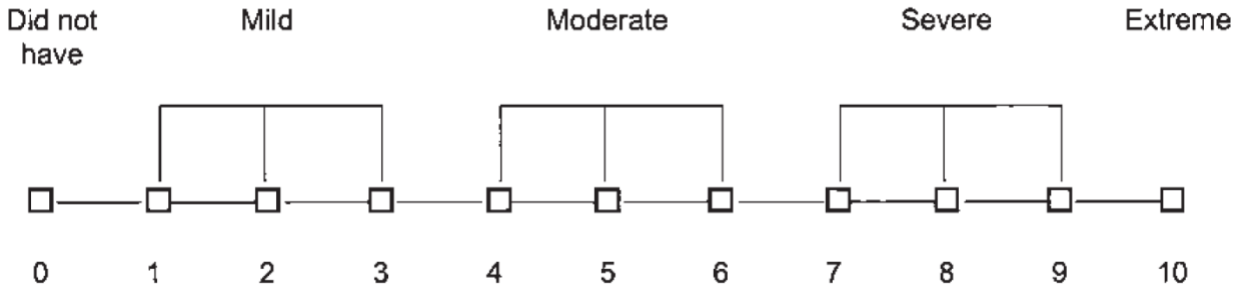
6. During the past 24 hours, how would you rate your flushing-related WARMTH?



7. During the past 24 hours, how would you rate your flushing-related TINGLING?



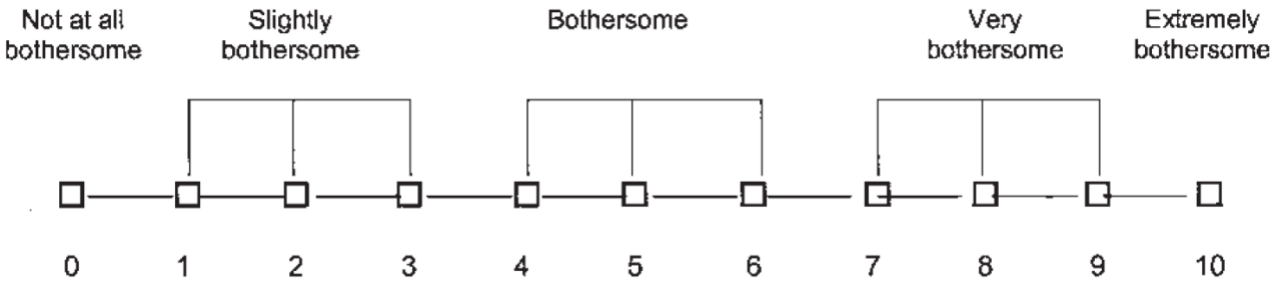
8. During the past 24 hours, how would you rate your flushing-related ITCHING?



The next questions refer to DIFFICULTY SLEEPING (either falling asleep or staying asleep) due to flushing symptoms last night.

9. Did flushing symptoms cause you to have difficulty sleeping last night? (response options: Y, N: if no, diary skipped to medication reminder)

10. How BOTHERSOME was it to have difficulty sleeping last night due to flushing?



Appendix 2 – Clinican's Erythema Assessment (CEA) And Patient's Self Assessment (PSA)

Will be handed out to patient to fill out daily during the study period.

Clinican's Erythema Assessment (CEA) And Patient's Self Assessment (PSA)

	CEA	**PSA**
0 = Clear	Clear skin with no signs of erythema	Clear of unwanted redness
1 = Almost clear	Almost clear; slight redness	Nearly clear of unwanted redness
2 = Mild	Mild erythema, definite redness	Somewhat more redness than I prefer
3 = Moderate	Moderate erythema; marked redness	More redness than I prefer
4 = Severe	Severe erythema; fiery redness	Completely unacceptable redness

Appendix 3 – Investigator's Global Assessment (IGA)

Grade	Score	Clinical description
Clear	0	No inflammatory lesions present, no erythema
Almost clear	1	Very few small papules/pustules, very mild erythema present
Mild	2	Few small papules/pustules, very mild erythema present
Moderate	3	Several small or large papules/pustules, moderate erythema
Severe	4	Numerous small and/or large papules/pustules, severe erythema

Appendix 4 – Rosacea Clinical Scorecard (RCS)

Rosacea Clinical Scorecard

Patient Name _____ Date:

_____

Primary features

Flushing (transient erythema)	Absent	Mild	Moderate	Severe
Nontransient erythema	Absent	Mild	Moderate	Severe
Papules and pustules	Absent	Mild	Moderate	Severe
Telangiectasia	Absent	Mild	Moderate	Severe

Secondary features

Burning or stinging	Absent	Mild	Moderate	Severe
Plaques	Absent	Mild	Moderate	Severe
Dry Appearance	Absent	Mild	Moderate	Severe
Edema	Absent	Mild	Moderate	Severe
If present:	Acute	Chronic		
If chronic	Pitting	Nonpitting		
Ocular manifestations	Absent	Mild	Moderate	Severe
Peripheral location	Absent	Present		
If present:	List location(s):			
Phymatous changes	Absent	Mild	Moderate	Severe
Granulomatous changes	Absent	Mild	Moderate	Severe

Global Assessment

Physician ratings by subtype

Subtype 1: Erythematotelangiectatic	Absent	Mild	Moderate	Severe
Subtype 2: Papulopustular	Absent	Mild	Moderate	Severe
Subtype 3: Phymatous	Absent	Mild	Moderate	Severe
Subtype 4: Ocular	Absent	Mild	Moderate	Severe
Patient's global assessment	Clear	Mild	Moderate	Severe

Initial symptoms occurred:

Treatments prescribed:

Comments:

Physician:

Appendix 5 – Rosacea-specific Quality-of-Life Index (RosaQoL)

S1 Table. The original version of rosacea-specific quality-of-life instrument

RosaQoL items
1. I worry that my rosacea may be serious ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
2. My rosacea burns or stings ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
3. I worry about getting scars from my rosacea ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
4. I worry that my rosacea may get worse ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
5. I worry about side effects from rosacea medications ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
6. My rosacea is irritated ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
7. I am embarrassed by my rosacea ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
8. I am frustrated by my rosacea ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

9. My rosacea makes my skin sensitive

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

10. I am annoyed by my rosacea

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

11. I am bothered by the appearance of my skin (redness, blotchiness)

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

12. My rosacea makes me feel self-conscious

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

13. I try to cover up my rosacea (with makeup)

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

14. I am bothered by persistence/reoccurrence of my rosacea

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

15. I avoid certain foods or drinks because of my rosacea

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

16. My skin feels bumpy (uneven, not smooth, irregular)

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

17. My skin flushes

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

18. My skin gets irritated easily (cosmetics, aftershaves, cleansers)

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

19. My eyes bother me (feel dry or gritty)

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

20. I think about my rosacea

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

21. I avoid certain environments (heat, humidity, cold)

because of my rosacea

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

Appendix 6– Dermatology Life Quality Index (DLQI)

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick one box for each question.

12.1 Over the last week, how itchy, sore, painful or stinging has your skin been?

☐ Very much ☐ A lot ☐ A little ☐ Not at all

12.2 Over the last week, how embarrassed or self conscious have you been because of your skin?

☐ Very much ☐ A lot ☐ A little ☐ Not at all

12.3 Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?

☐ Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant

12.4 Over the last week, how much has your skin influenced the clothes you wear?

☐ Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant

12.5 Over the last week, how much has your skin affected any social or leisure activities?

☐ Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant

12.6 Over the last week, how much has your skin made it difficult for you to do any sport?

☐ Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant

12.7 Over the last week, has you skin prevented you from working or studying?

☐ Yes ☐ No ☐ Not relevant

If "No", over the last week how much has your skin been a problem at work or studying?

☐ Very much ☐ A lot ☐ A little ☐ Not at all

12.8 Over the last week, how much has your skin created problems with your partner, or any close friends or relatives?

☐ Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant

12.9 Over the last week, how much has your skin caused any sexual difficulties?

☐ Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant

12.10 Over the last week, how much pf a problem has the treatment for your skin been, for example by making your home messy, or taking up time?

☐ Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant

Appendix 7 – Hospital Anxiety and Depression Scale (HADS)

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

Appendix 8 – Quick Inventory of Depressive Symptomatology (QIDS)

QUICK INVENTORY OF DEPRESSIVE SYMPTOMATOLOGY (SELFREPORT)

(QIDS-SR 16)

Please circle the one response to each item that best describes you for the past seven days.

1. Falling asleep:

0 I never take longer than 30 minutes to fall asleep.

1 I take at least 30 minutes to fall asleep, less than half the time.

2 I take at least 30 minutes to fall asleep, more than half the time.

3 I take more than 60 minutes to fall asleep, more than half the time.

2. Sleep during the night:

0 I do not wake up at night.

1 I have a restless, light sleep with a few brief awakenings each night.

2 I wake up at least once a night, but I go back to sleep easily.

3 I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.

3. Waking up too early:

0 Most of the time, I awaken no more than 30 minutes before I need to get up.

1 More than half the time, I awaken more than 30 minutes before I need to get up.

2 I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually.

3 I awaken at least one hour before I need to, and can't go back to sleep.

4. Sleeping too much:

0 I sleep no longer than 7–8 hours/night, without napping during the day.

1 I sleep no longer than 10 hours in a 24-hour period including naps.

2 I sleep no longer than 12 hours in a 24-hour period including naps.

3 I sleep longer than 12 hours in a 24-hour period including naps.

5. Feeling sad:

0 I do not feel sad.

1 I feel sad less than half the time.

2 I feel sad more than half the time.

3 I feel sad nearly all of the time.

6. Decreased appetite:

0 There is no change in my usual appetite.

1 I eat somewhat less often or lesser amounts of food than usual.

2 I eat much less than usual and only with personal effort.

3 I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.

7. Increased appetite:

0 There is no change from my usual appetite.

1 I feel a need to eat more frequently than usual.

2 I regularly eat more often and/or greater amounts of food than usual.

3 I feel driven to overeat both at mealtime and between meals.

8. Decreased weight (within the last two weeks):

0 I have not had a change in my weight.

1 I feel as if I've had a slight weight loss.

2 I have lost 2 pounds or more.

3 I have lost 5 pounds or more.

9. Increased weight (within the last two weeks):

0 I have not had a change in my weight.

1 I feel as if I've had a slight weight gain.

2 I have gained 2 pounds or more.

3 I have gained 5 pounds or more.

10. Concentration/Decision making:

0 There is no change in my usual capacity to concentrate or make decisions.

1 I occasionally feel indecisive or find that my attention wanders.

2 Most of the time, I struggle to focus my attention or to make decisions.

3 I cannot concentrate well enough to read or cannot make even minor decisions.

11. View of myself:

0 I see myself as equally worthwhile and deserving as other people.

1 I am more self-blaming than usual.

2 I largely believe that I cause problems for others.

3 I think almost constantly about major and minor defects in myself.

12. Thoughts of death or suicide:

0 I do not think of suicide or death.

1 I feel that life is empty or wonder if it's worth living.

2 I think of suicide or death several times a week for several minutes.

3 I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.

13. General interest:

0 There is no change from usual in how interested I am in other people or activities.

1 I notice that I am less interested in people or activities.

2 I find I have interest in only one or two of my formerly pursued activities.

3 I have virtually no interest in formerly pursued activities.

14. Energy level:

0 There is no change in my usual level of energy.

1 I get tired more easily than usual.

2 I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking or going to work).

3 I really cannot carry out most of my usual daily activities because I just don't have the energy.

15. Feeling slowed down:

0 I think, speak, and move at my usual rate of speed.

1 I find that my thinking is slowed down or my voice sounds dull or flat.

2 It takes me several seconds to respond to most questions and I'm sure my thinking is slowed.

3 I am often unable to respond to questions without extreme effort.

16. Feeling restless:

0 I do not feel restless.

1 I'm often fidgety, wringing my hands, or need to shift how I am sitting.

2 I have impulses to move about and am quite restless.

3 At times, I am unable to stay seated and need to pace around.

Appendix 9 – Six-item Headache Impact Test (HIT-6)

		Never = 6	Rarely = 8	Sometimes = 10	Often = 11	Always = 13
1	When you have headache, how often is it very severe?					
2	How often does headache limit your ability to perform daily tasks including household, work, study, social activities?					
3	When you have a headache, how often do you feel like lying down?					
4	During the past 4 weeks, how often have you felt too tired to work or perform daily tasks due to headache?					
5	During the past 4 weeks, how often have you felt demotivated or annoyed due to headache?					
6	During the past 4 weeks, how often has your headache limited your ability to focus at work or during daily activities?					

Score: _____

Appendix 10 – Headache Reporting

Answer the following questions each day

1) Have you had a headache (including migriane) during the past 24 hours?

☐yes ☐no

If yes, please answer the following questions.
If no, you don't need to anwer any more questions in this quesionnaire.

2) How many times during the past 24 hours have you had a headache?
☐1
☐2
☐3
☐4
☐> 5

3) How long was your longest headache?
☐< 30 minutes
☐30 minutes til 3 hours
☐4 hours to 12 hours
☐> 12 hours

If the headache lasted less than 30 minutes you don't have to answer any more questions.

In the following questions, please refer to the worst headache you have had within the past 24 hours.

4) How long did your worst headache last?

☐< 30 minutes

☐30 minutes til 3 hours

☐4 hours to 12 hours

☐> 12 hours

5) What the headache unilateral or bilateral?

☐Unilateral ☐Bilateral

6) How bad was the headache when it was at its worst(0=no pain, 10=worst imaginable pain)?

☐ 0

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

7) Was the headache pressing or throbbing?

☐Pressing ☐Throbbing

8) Did you feel nauseous?

☐Yes ☐No ☐Vomited

9) Did you feel sensitive to light?

☐Yes ☐No

10) Did you feel sensitive to sound?

☐Yes ☐No

11) Did it feel like a regular migriane?

☐Yes ☐No

12) Did you take any medication for your headache?

☐Yes ☐No

If yes,

What did you take:

When:

Which dose:

Did you have an effect from the medication?

☐Yes ☐No

13) Did you have visual or sensory disturbances?

☐yes ☐no

14) Did you experience anything else in relation to the headache?

☐yes ☐no

If yes, please elaborate_____