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Pilot 2 diabetes

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CLINICAL INVESTIGATION PLAN
Including substantial amendment 2

Evaluation of the hypoglycaemia alarm device hyposafe H02 – the pilot 2 study – in subjects with type 1 diabetes

A 4-month non-controlled observational study

Investigational device	**hyposafe H02**
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Manufacturer	**UNEEG™ medical A/S** Borupvang 2 DK-3450 Allerød Denmark Tel : +45 4063 8000 www.uneeg.com

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List of abbreviations

ADE:	Adverse device effect
AE:	Adverse event
BG:	Blood glucose
°C:	Centigrade
CA:	Competent authority
CIP:	Clinical investigation plan
CGM:	Continuous glucose monitoring
CRA:	Clinical research associate
CRF:	Case report form
CRO:	Contract research organisation
EC:	Ethics committee
ECG:	Electrocardiogram
EEG:	Electroencephalogram
FAS:	Full analysis set
HV:	Healthy volunteers
ISO:	International standard organisation
MedDRA:	Medical dictionary for regulatory activities
PG:	Plasma glucose
PP:	Per protocol
SADE:	Serious adverse device effect
SAE:	Serious adverse event
SOC:	Standard operation classification
TEAE:	Treatment emergent adverse events
V:	Voltage

1 Background information and justification for conducting the study

1.1 Background

1.1.1 Hypoglycaemia in patients with type 1 diabetes

The near-normalisation of glucose levels has become an established goal in diabetes treatment in order to reduce the risk of late complications such as nephropathy, neuropathy, retinopathy and cardiovascular disease (1). The fear of hypoglycaemia, the most common adverse event (AE) associated with insulin treatment in patients with diabetes (2), discourages patients from maintaining tight glycaemic control and only a minority of the patients reach the defined goal of glucose control, leading to increased diabetes related morbidity and mortality (3–7). Symptoms of hypoglycaemia can be classified as autonomic (warning) symptoms caused by the release of catecholamines, or neuroglycopenic symptoms caused by the lack of glucose supply to the brain. Following long-term diabetes duration and tight glycaemic control, autonomic symptoms may be

compromised due to impaired glucose counter regulatory response. Between 1/4 and 1/3 of patients with type 1 diabetes suffer from impaired awareness or unawareness to hypoglycaemia (5,8,9).

1.1.2 A hypoglycaemia alarm based on electroencephalography

The electroencephalogram (EEG) reflects the functional state and metabolism of the brain. The brain is critically dependent on a continuous supply of glucose, and when the glucose level is lower than the metabolic requirements of the brain, brain function deteriorates. Neuroglycopenic hypoglycaemia in insulin-treated patients with diabetes is associated with characteristic changes in EEG, including a decrease in alpha activity and an increase in delta and theta activity (10–13). These changes are clearly seen at blood glucose level of ~2.0 mmol/L (10,11) preceding the development of severe cognitive dysfunction (14).

Sleep EEG differs significantly from daytime EEG with periods of deep sleep defined by the presence of slow wave dominance. Approximately 50% of all hypoglycaemic episodes occur during sleep, and prolonged episodes of hypoglycaemia as measured by continuous glucose monitoring (CGM) occur in 8.5% of all nights in both children and adults (15).

For the device to have clinical applicability, it should be able to distinguish hypoglycaemia-induced EEG changes from noise, artefacts and physiological variations in the EEG including the low-frequency waves seen during sleep, with high sensitivity and specificity using an algorithm that classifies the EEG in real-time. There should be a timely difference between hypoglycaemia-induced EEG changes and severe cognitive impairment. The device must be fully compatible with everyday activities. Thus, the device should be small, biocompatible and implantable, and the monitoring and processing unit should be small and have sufficient battery power.

1.2 Rationale for study

While a finger prick test accurately measures the blood glucose level, it does not provide continuous measurements, and hence it is unreliable as a hypoglycaemia alarm. Recent studies have indicated that the use of CGM reduces the risk of severe hypoglycaemia (19). However, some find these devices troublesome to use and are annoyed by the inaccuracy of the measurements, and even after short term use the coverage in subgroups of patients is as low as 50% of the time (20–22). Thus there is a medical need for a reliable hypoglycaemia alarm which is easy and convenient to use and with high sensitivity and high rate of positive prediction.

The current protocol describes a clinical study designed to evaluate the sensitivity and the positive predictive value of the hyposafe H02 in subjects with type 1 diabetes during everyday activities and during insulin-induced hypoglycaemia. In addition, information regarding safety and usability will be collected and analysed. This is to verify that the hyposafe H02 is working as intended in subjects with type 1 diabetes before proceeding with the planned larger study in subjects with type 1 diabetes.

2 Study objectives and endpoints

2.1 Objectives

2.1.1 Primary objectives

Performance

To evaluate the technical performance of the hyposafe H02 during everyday activities and during insulin-induced hypoglycaemia in subjects with type 1 diabetes.

Safety

To evaluate potential safety issues associated with the implantation and use of the hyposafe H02 in subjects with type 1 diabetes.

2.1.2 Secondary objective

Usability

To evaluate the usability of the hyposafe H02 during everyday activities in subjects with type 1 diabetes.

2.2 Endpoints

Primary performance endpoints

- Sensitivity: Proportion of spontaneous hypoglycaemic episodes detected by the hyposafe H02 compared to the total number of validated[1] spontaneous hypoglycaemic episodes after 12 weeks of monitoring (from visit 5 to visit 10)
- Positive predictive value: Proportion of validated[1] spontaneous hypoglycaemic episodes detected by the hyposafe H02 compared to the total number of alerts from the hyposafe H02 after 12 weeks of monitoring (from visit 5 to visit 10)

Secondary performance endpoints

- Overall sensitivity: Overall proportion of hypoglycaemic episodes detected by the hyposafe H02 compared to the total number of validated[2] hypoglycaemic episodes after 12 weeks of monitoring (from visit 5 to visit 10)
- Overall positive predictive value: Overall proportion of validated[2] hypoglycaemic episodes detected by the hyposafe H02 compared to the total number of alerts from the hyposafe H02 after 12 weeks of monitoring (from visit 5 to visit 10)
- Sensitivity: Proportion of insulin-induced hypoglycaemic episodes detected by the hyposafe H02 compared to the total number of insulin-induced hypoglycaemic episodes

[1] Validated by self-measured blood glucose (SMBG) or clinical hypoglycaemia according to subject's experience
[2] Validated by self-measured blood glucose (SMBG), plasma glucose (PG) or clinical hypoglycaemia according to subject's experience

- Positive predictive value: Proportion of insulin-induced hypoglycaemic episodes detected by the hyposafe H02 compared to the total number of alerts from the hyposafe H02
- Number of participants with a satisfactory EEG Quality test
- Change in impedance (from visit 5 to visit 10)
- Number of device complaints (from visit 4 to visit 10)
- Mean glucose level at the time of a hypoglycaemia alarm

Primary safety endpoint

- Number of AEs 17 weeks after implantation (from visit 3 to visit 12)

Secondary safety endpoint

- Number of adverse device effects (ADEs) 17 weeks after implantation (from visit 3 to visit 12)

Secondary usability endpoints

- Development in discomfort over time (visit 5 to visit 10)
- User satisfaction (visit 8)
- Mean number of hours of use per hyposafe H02 device (from visit 4 to visit 10)
- Response to hypoglycaemia alarm (from visit 5 to visit 10)
- Assessment of alarm fatigue (visit 12)

3 Study design - overview

3.1 Description of study design

The present study is a 4-month non-controlled observational study in subjects with type 1 diabetes. Subjects will attend a screening visit (visit 1) in order to assess their eligibility, followed by an inclusion visit (visit 2) which should take place as soon as all screening results (including laboratory results) are available, reviewed and the subject is confirmed eligible. 12-20 subjects are planned to be enrolled, and withdrawals will be replaced until at least 12 subjects have completed the study.

The subjects will have the implantable part of the hyposafe H02 device implanted (see Figure 1). Subjects will be exposed to insulin-induced hypoglycaemia twice during the study. A device for continuous glucose monitoring (CGM) will be mounted for two periods of approximately 5 days. They will wear the hyposafe H02 device as much as possible both during daytime and night-time. In addition, they will fill out questionnaires and complete an interview regarding use, discomfort and satisfaction related to the implantation and the use of the H02 device.

Subjects will have the implantable part of the hyposafe H02 device implanted at visit 3 by a surgical procedure under local anaesthesia. External parts of the hyposafe H02 device will be mounted at visit 4 and fitted if needed at each subsequent visit until visit 10 (see flow chart Table 1).

The duration of the study from screening (visit 1) to removal of sutures (visit 12) will be approximately 18 weeks.

This study will be conducted in accordance with this investigational plan, ISO 14155:2011, ethics committee requirements, the Declaration of Helsinki (23), applicable local governmental regulations, and appropriate regulations for clinical studies.

4 Study population

4.1 Definition of the overall subject population

Between 12 and 20 subjects with type 1 diabetes and impaired awareness of hypoglycaemia will be enrolled in the study to ensure a number of subjects completing the study of at least 12.

4.2 Inclusion criteria

For a subject to be eligible, all inclusion criteria must be answered "yes":

1. Informed consent obtained before any study related activities[3]
2. Type 1 diabetes diagnosed at least five years prior to inclusion in the study
3. Age 18-70 years
4. Impaired awareness, i.e. defined as unaware by the Pedersen-Bjergaard scale (section 6.1.5) *and/or* history of at least one severe hypoglycaemia[4] within the preceding year

4.3 Exclusion criteria

For a subject to be eligible, all exclusion criteria must be answered "no":

1. Severe cardiac disease
    - History of myocardial infarction
    - Cardiac arrhythmia
2. History of stroke or cerebral haemorrhage and any other structural cerebral disease
3. Active cancer or cancer diagnosis within the past 5 years
4. Uraemia defined as s-creatinine ≥ 3 times upper reference value
5. Liver disease defined as s-ALAT ≥ 3 times upper reference interval
6. Epilepsy
7. Use of antiepileptic drugs for any indication
8. Clinically important hearing impairment
9. Use of active implantable medical device including
    - Pacemaker and ICD-unit
    - Cochlear implant
10. Use of following drugs:

[3] A study related activity is any procedure that would not have been performed during the normal management of the subject

[4] Requiring assistance from third person whether being help for carbohydrate ingestion, glucagon injection or contact to health care person

- Chemotherapeutic drugs of any kind
- Methotrexate
- Third generation antipsychotic drugs (aripiprazole, quetiapine, clozapine, ziprasidone, paliperidone, risperidone, sertindole, amisulpride, olanzapine)

11. Contraindications to the local anaesthetic used during implantation (1% xylocain with adrenalin)
12. Known or suspected abuse of alcohol defined as consumption of >250g alcohol[5] or any other neuro-active substances
13. Infection at the site of device implantation
14. Any haemorrhagic disease
15. Females of childbearing potential who are pregnant or intend to become pregnant or are not using adequate contraceptive methods[6] throughout the study
16. Performing extreme sport, including scuba diving (snorkel diving is allowed) or parachute jumping
17. Incapable of understanding the subject information or unlikely to complete the study for any reason
18. Operating MRI scanners
19. Operating handheld transceivers for communication (e.g. within the police, medical, fire, air traffic control, marine or military)
20. Working at broadcast stations for television or FM/DAB radio

Subjects who are non-compliant with any of the eligibility criteria, but included in the study, should be excluded immediately. If extraordinary circumstances speak in favour of maintaining the subject in the study then this is only acceptable if justified and approved by the ethics committee and if regulatory authorities are notified.

4.4 Withdrawal criteria

1. The subject may withdraw at will at any time without explanation
2. The subjects may be withdrawn from the study at the discretion of the investigator due to a safety concern or if judged non-compliant with the study procedures

Subjects must be withdrawn from the study for any of the following reasons:

3. Included in the study in violation with any of the inclusion and/or exclusion criteria
4. Use of any drug listed under exclusion criteria
5. Subject becomes pregnant during the study

This will not impact the treatment or follow-up of the subject. If a subject is withdrawn from the study, the investigator must aim to undertake procedures similar to those for visit 11 and 12: The

[5] in Danish: 21 “genstande” per week
[6] Safe anticonceptive methods includes contraceptive pills, intrauterine device including hormone intrauterine device and sustained gestagen injection

device must be explanted as quickly as possible, the sutures removed when appropriate and the end-of-study-form in the case report form (CRF) must be filled out.

Although a subject is not obliged to give his/her reason(s) for withdrawal, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Any reasons obtained must be specified in the subject's medical file and the appropriate section of the CRF.

5 Description of the hyposafe H02 device

The hyposafe H02 device consists of three parts: An implantable part which consists of a 20 mm semi-spherical implant house and an electrode (diameter: 1 mm, length 100 mm), see Figure 1b. The implant records the EEG signal and transmits the signal wirelessly to the external device. The position of the implant is depicted in Figure 1a. The external device is supplied in two versions: An ear hanger (Figure 1c) and a disc version (Figure 1d) both wirelessly receiving signals from the implant and charging the implant. An insertion needle for the implantation procedure (Figure 1e).

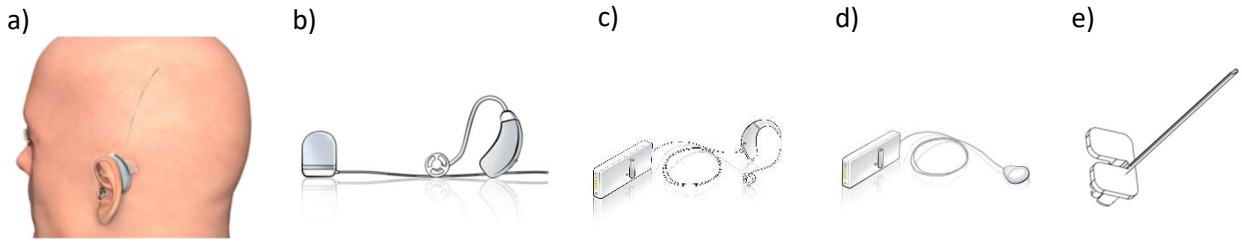

Figure 1 Hyposafe H02 device

a) Position of the implant and the external part of the device, b) The implant (left) consists of an electrode and an implant house. The external part (right) demonstrates the earhanger alone, c) Earhanger version of the external device, d) Disc version of the external device, e) Needle for insertion of the electrode

6 Methods and assessments

6.1 Visit procedures

Procedure for scheduled visits and telephone contacts are described in the following and in the flow chart (Table 1).

Table 1 Flow chart

Visit number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12
Time related to time of implantation (weeks)	-0.5	0[1)]	0	1.5	3	4	5	7	11	15	16	17
Visit window (days)				±2[2)]	±5	±5	±5	±5	±5	±5	±7[4)]	[2)]
Name of visit	Screening	Inclusion	Implantation	Device mounting	Start-up visit	One-week observation	Two weeks observation	Four weeks observation	Eight weeks observation	End of study	Device explantation	Follow-up
Screening, Informed consent	X											
Safety blood measurements	X											
Concomitant illness/medical history	X											
Demography	X											
Physical examination	X				X					X		
ECG	X											
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
In/exclusion criteria	X	X										
Withdrawal criteria			X	X	X	X	X	X	X	X		
Device implantation			X									
Suture removal				X								X
Photography of device fitting					X							
EEG quality test					X					X		
CGM mounting					X				X			
Mounting of external device				X								
Collecting data for calibration start				X								
Hypoglycaemia alarm “on”					X	X	X	X	X	X		
Adverse events registration			X	X	X	X	X	X	X	X	X	X
Adverse device effect registration				X	X	X	X	X	X	X	X	X
Induced hypoglycaemia							X			X		
Log book				X	X	X	X	X	X	X		
Questionnaire					X			X		X		
Device explantation											X	
Surgeon questionnaire			X								X	
UNEEG™ medical staff present			X[7)]	X[7)]	X[7)]	X[7)]	X[7)]	X[7)]	X[7)]	X[7)]	X[7)]	X

[1)] Inclusion should take place as soon as all screening (including laboratory results) are available, reviewed and subject is confirmed eligible and no later than two weeks after screening. This visit can be performed as a telephone consultation after reviewing blood samples

[2)] Removal of sutures should be within a time window of 8-12 days following implantation and explantation, respectively

[4)] The explantation of the implanted device should take place as soon as possible following the end of study visit

[7)] Optional

6.1.1 Early discontinuation

In case of early discontinuation, either requested by the subject or at the discretion of the investigator, the end-of-study-form must be completed. The subject must be followed up, as appropriate.

6.1.2 Adverse events

6.1.2.1 Definitions

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a subject whether related to the device or not.

This includes events from the first study related activity after subject has signed the informed consent and until removal of sutures (visit 12), see flow chart Table 1.

A worsening in concomitant illness must be recorded as an AE. A worsening of an ongoing AE should be recorded on a new AE form by making a new assessment for seriousness and possible relationship to hyposafe H02 device or implantation procedure.

Adverse device effect

An adverse device effect (ADE) is defined as any untoward and unintended response to a medical device including insufficiencies or inadequacies in instructions for use or deployment, the implantation, the operation, or any malfunction of the investigational medical device. This also includes any event that is a result of a use error or intentional misuse of the device.

Serious adverse event

An serious adverse event (SAE) is defined as an AE that results in any of the following:

- Death
- A life-threatening experience[7]
- In-subject hospitalisation or prolongation of existing hospitalisation
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

Serious adverse device effect

Serious adverse device effect (SADE) is defined as an ADE that has resulted in any of the consequences characteristics of a SAE or that might have led to any of these consequences if suitable action had not been taken, intervention had not been made or if circumstances had been less fortunate. These are handled under the SAE reporting system.

[7] The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe

6.1.2.2 Collection, recording and reporting of adverse events

All events meeting the definition of an AE/ADE must be collected and reported. During each contact with the site (site visit or telephone contact) the subject must be asked about AEs/ADE.

The sponsor will discuss with the investigator all SAEs/SADEs and co-ordinate appropriate actions. Investigator will be informed of any study related procedure SAEs/SADEs that may warrant a change in any study procedure. If the sponsor or the safety committee find continuation of the study incompatible with the safety of the study subjects due to any safety issues related to the hyposafe H02 or the study procedures, the study will be terminated or postponed until these issues have been solved.

UNEEG™ medical must report all SAEs/SADEs to the ethics committee and the Danish Health and Medicines Authority according to the national regulations.

6.1.2.3 Follow-up of adverse events

During and following a subject's participation in a clinical study, the investigator should ensure that adequate medical care is provided for any subject for any AE.

6.1.3 Concomitant illness/medical history

A concomitant illness is any illness that is present at the start of the study (visit 1) or found as a result of the screening procedure. Medical history is a medical event that the subject has experienced in the past. Any changes in the concomitant illness should be recorded during the study. A clinically significant worsening of a concomitant illness must be reported as an AE (see section 6.1.2.2).

6.1.4 Concomitant medication

Concomitant medication is any medication, which is taken during the study. Detail on concomitant medication must be recorded at visit 1. Changes in concomitant medication must be recorded at each visit as they occur.

6.1.5 Hypoglycaemia awareness status

The Pedersen-Bjergaard method (24) and recent history of severe hypoglycaemia will be used to assess hypoglycaemia awareness status at visit 1.
For the Pedersen-Bjergaard method, the subject will be asked: "Do you recognise symptoms when you have a hypo?" and can select one of the following answers:

- Always
- Usually
- Occasionally
- Never

Subjects answering "occasionally" or "never" (i.e. unaware according to Pedersen-Bjergaard method) *and/or* who has experienced at least one severe hypoglycaemic episode within the preceding year will be classified as having impaired awareness of hypoglycaemia.

6.2 Case report forms

Case report forms (CRFs) are provided in a uniform design, each form heading requires identification of the hospital, subject and investigator and each visit must be dated. The investigator must ensure that data are recorded in the CRF as soon as possible after the visit. Completed CRFs must be reviewed and signed by the local investigators. The CRF must be kept on site until the designated CRA has performed verification of all data entries.

6.3 Traceability and recording of the investigational device

At the site, a device accountability system will be maintained during the study, documenting device shipment and receipt, storage at the site, use, and return to the sponsor of used/unused devices, as applicable.

6.4 Monitoring

The sponsor will appoint a qualified, experience and trained Clinical Research Associate (CRA) from the Contract Research Organisation (CRO) who will visit the study centre periodically during the study. The CRA is to ensure adherence to the clinical investigation plan, including verification of subject informed consent, letter of authorisation, inclusion and exclusion criteria etc. The CRA should also verify and review all AEs/ADEs and SAEs/SADEs.

Investigators must provide access to the hospital files and any other medical source document containing subject's clinical/medical information, to the CRA for them to perform source document verification. The CRA is responsible for verifying the data entered into the CRFs against hospital source documents to ensure accuracy and completeness of the data, prior to retrieving the CRFs, from the study centre.

During the study CRA must check that appropriate written informed consents and power of attorney have been obtained. The CRA must inform the sponsor about any problems relating to facilities, technical equipment or medical staff at the study centre. The CRA must notify such deficiencies in writing to the related clinical centre's principal investigator and convene with the study centre personnel appropriate and timely corrective actions. The CRA must make written reports to the sponsor, after each visit or contact with the investigator or centre.

6.5 Data management

Data management is the responsibility of UNEEG™ medical but may be delegated under an agreement of transfer of responsibilities to a CRO. Data collected via the CRFs will be subject to data quality control measures in compliance with all applicable data management procedures. All CRFs will be audited against corresponding database output to ensure accuracy. Data management will correct obvious errors, and a query will be sent to the CRA for confirmation of the correction by the investigator, as will queries for omission and discrepancies or other errors. The CRFs will be corrected as required and the corrected data entered into the database. The copy of the signed query form will be filed with the CRFs.

Prior to database lock the database will be validated. When all queries have been resolved, the database will be locked. Any changes to the database after that time will require joint written agreement between the investigator, the biostatistician and the sponsor.

7 Statistical considerations and data reporting

Tabulations and cross-tabulations will be performed as outlined in the endpoint analysis section. No comparative statistical analyses are planned. Any deviations from the planned statistical analysis will be justified in the study report.

7.1 Rational for the choice of sample size

This is not a comparative endpoint study. It is assumed that sufficient information about the performance, safety and the use of the hyposafe H02 to support any potential optimisation of the algorithm or adjustment of procedures will be obtained with approximately 12 subjects with type 1 diabetes. The total number will depend on the results of the study and number of withdrawals, and it is planned to enrol 12-20 subjects with type 1 diabetes to ensure a number of subjects completing the study of at least 12.

7.2 Definition of analysis populations

The following analysis set are defined according: Full analysis set (FAS) are all subjects included in the study will be included in the FAS. Per protocol (PP) analysis set are all subjects of the FAS who completed the trial without major protocol violations will be included in the PP analysis set. Safety analysis set are all subjects in whom the investigational device was implanted will be included in the safety analysis set

7.3 Demographics and baseline characteristics

Demographic and baseline characteristics will be summarised according to the type of data. Summaries will be provided for entire study population.

7.4 Handling of missing data

Subjects who withdraw from the study due to reasons not related to the hyposafe H02 device will be tabulated with the reasons for the withdrawal.

7.5 Endpoint analysis

7.5.1 Performance endpoints

All performance endpoints will be analysed using the FAS as well as the PP analysis set.

Primary performance endpoint

The primary performance endpoints are defined as the sensitivity and positive predictive value of the hyposafe H02 based on spontaneous hypoglycaemic episodes.

Spontaneous hypoglycaemic episodes are recorded by subjects in the log book throughout the study. This includes information on blood glucose measurements before treating the episode, alarms given by the hyposafe H02 device and information on whether the subjects was able to treat him/herself or was asleep when the episode occurred.

A hypoglycaemic episode will be characterised as treatment emergent if the onset of the episode is on or after the first day the hyposafe H02 device switched to "*alarm on"*-mode and no later than the last day of the wearing the external device. Data on treatment emergent hypoglycaemic episodes are presented in terms of the number of subjects with at least one episode (N) and the number of episodes (E).

Hypoglycaemic episodes will be defined as nocturnal (i.e. during night-time) if they occur during sleep (as reported by the subject) and/or are registered by the hyposafe H02 night device.

Data from blood glucose measurement and clinical hypoglycaemia (according to subject's experience) will be used by UNEEG™ medical to classify a hypoglycaemic alarm according to categorisation displayed in Table 2 (true and false, positive and negative hypoglycaemia alarms). As blood glucose values are lower than plasma values, a constant factor of 1.11 is used to convert concentration in whole blood to the equivalent concentration in plasma (25).

Sensitivity and positive predictive value will be calculated for daytime and night-time, separately.

Secondary performance endpoints

Insulin-induced hypoglycaemia is performed twice for each subject, with frequent assessments of plasma glucose levels. As the number of spontaneous hypoglycaemic episodes reported during the study may be relatively small, data from the insulin-induced hypoglycaemia will be added to calculate the overall **sensitivity and positive predictive value** of the hyposafe H02 (spontaneous and insulin-induced hypoglycaemia episodes) after 12 weeks of monitoring (from visit 5 to visit 10).

The sensitivity and positive predictive value will also be calculated based data from the insulin-induced hypoglycaemic episodes only.

The hypoglycaemic alarms will be classified according to categorisation displayed in Table 2 (true and false, positive and negative hypoglycaemia alarms), and presented as described for primary performance endpoint.

Table 2 Categorisation of hypoglycaemic episodes

Episodes categorised as			
PG > 3.9mmol/l	+ alarm	+/- clinical hypoglycaemia[a)]	False positive □
	- alarm	+/- clinical hypoglycaemia [a)]	True negative □
PG 2.0 – 3.9mmol/l	+ alarm	+/- clinical hypoglycaemia [a)]	True positive □
	- alarm	+ clinical hypoglycaemia [a)]	False negative □
		- clinical hypoglycaemia [a)]	True negative □
PG < 2.0mmol/l	+ alarm	+/- clinical hypoglycaemia [a)]	True positive □
	- alarm	+/- clinical hypoglycaemia [a)]	False negative □
PG not measured	+ alarm	+ clinical hypoglycaemia [a)]	True positive □
		- clinical hypoglycaemia [a)]	Not categorised □
	- alarm	+ clinical hypoglycaemia [a)]	Not categorised
			False negative[b)]

[a)] According to subject (No strict definition is given)

[b)] If hypoglycaemic episode was severe (i.e. requiring assistance from third person whether being help for carbohydrate ingestion, glucagon injection or contact to health care person), the episodes should be characterised as false negative

PG; plasma glucose

Data from **EEG quality test** at the visit 4 and visit 10 will be compared graphically.

The **impedance** is expected to be below 5 kOhm at all times. No trend in the measurements for each subject should be apparent over time, except perhaps a small decline in the beginning. Any change in impedance over time (from visit 5 to visit 10) will be summarised descriptively and presented by subject.

The **number of device complaints** will be tabulated and presented by device part.

Mean blood, plasma or interstitial **glucose level at the time of an alarm** will be summarised for insulin-induced hypoglycaemia and spontaneous hypoglycaemic episodes, separately.

7.5.2 Safety endpoints

All safety endpoints will be analysed using the safety analysis set.

Primary safety endpoint

The primary safety endpoint is defined as the number of AEs 17 weeks after implantation.

All AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA).

Secondary safety endpoint

The number of **ADEs** 17 weeks after implantation will be summarised as described for AEs.

7.5.3 Usability endpoints

All usability endpoints will be analysed using the FAS.

Development in discomfort over time

Data from questionnaires regarding discomfort related to the implanted device will be tabulated and presented by week and discomfort category and compared over time (visit 5 to visit 10).

Assessment of alarm fatigue

Data from questionnaire regarding alarm fatigue at visit 12 will be tabulated and presented by category of sensitivity and false alarm(s).

User satisfaction

Subject user satisfaction at visit 8 will be summarised based on the specific questionnaire.

Usage of external device

The mean number of hours the hyposafe H02 day or night device has been connected to the implant from visit 4 to visit 10 will be summarised. Summaries will be presented for daytime and night-time, separately.

Response to hypoglycaemia alarm

The number of preventive actions, i.e. the number of hypoglycaemia alarms where subject was able to take preventive action as instructed (acknowledge the alarm by key press, measure blood glucose, and in case of low blood glucose; ingest a carbohydrate rich meal) compared to the total number of hypoglycaemia alarms from visit 5 to visit 10 will be tabulated.

8 Ethics

The study will be conducted according to the Declaration of Helsinki (23) and approved by the local ethical committee before commencement. The use of the hyposafe H02 must be approved by the Danish Health and Medicines Agency before initiation. Only information relevant for the study will be collected. As UNEEG™ medical is a private data responsible the current private health research project will not been notified to the Danish Data Protection Agency. Data will be handled in accordance with the Act on Processing of Personal Data.

8.1 Subject benefit and risks

A risk analysis according to ISO 14971 “Application of risk management to medical devices” has been conducted. Risks have been minimised or eliminated through appropriate design control.

Impaired awareness of hypoglycaemia associated with increased morbidity and mortality, is a serious problem for many patients with type 1 diabetes, and it is believed that the potential benefit of a hypoglycaemia alarm system overweighs the potential risks in the current study.

The subject participating in this study cannot be guaranteed benefits of the participation. If the hypoglycemia alarm works as intended, subjects with the alarm function switched on may experience an increased security at hypoglycaemia.

An external energy source powers the implant via an inductive link. There is no risk of transfer of power from the energy source to the surrounding tissue of the subject. No radioactive substances are used in the study.

Foreseeable AEs and anticipated ADEs are infection (estimated risk: 0.5%), headache (estimated risk: 10%), seizures (estimated risk: 0.5%), and phlebitis (estimated risk: 1-2%).

8.2 Subject insurance

Product liability and no fault clinical trial assurance covering the duration of the study are in place, to enable compensation in the event of an injury to a participating subject.

8.3 Informed consent

Study subjects will be recruited by advertising or by personal contact to the subject in the outpatient clinics. The information sheet will be sent to or given to the participant at least 3 days before the screening visit. Participants will be encouraged to bring a friend or a family member for the screening visit at the study site. The study procedures will be explained to the participant by qualified personnel and the information sheet will be reviewed with the participant under undisturbed conditions in a quiet room reserved for this purpose. A voluntary, signed and dated informed consent form must be obtained from the subject prior to any study related activities.

The investigator is responsible for ensuring that no subject is subjected to any study related examination or activity before the subject has given his/her written informed consent. The written informed consent must be signed and dated by the person who seeks the consent.

8.4 Early termination or suspension of the investigation

If the sponsor or the safety committee find continuation of the study incompatible with the safety of the study subjects due to any safety related issues of the study product or the study procedure the study will be terminated or postponed until these issues have been solved.

If a study is prematurely terminated or suspended, the investigator should promptly inform the subjects and assure appropriate follow-up. Furthermore, the investigator and/or UNEEG™ medical should promptly inform the ethics committee and provide a detailed written explanation. The regulatory authorities should be informed according the regulations.

8.5 Changes to clinical investigation plan or related procedures

All substantial changes to the clinical investigational plan must not be implemented before approval/favourable opinion unless necessary to eliminate immediate hazards to the subjects. All changes to the clinical investigation plan require notification to the ethics committee and the

competent authority. No changes in the study procedures must be implemented without mutual agreement of the investigator and the sponsor.

8.6 Deviations from clinical investigation plan

Deviation to the clinical investigational plan should be avoided. If deviations occur, the investigator must inform the sponsor who is responsible for analysing and assessing the implication of the deviation. Any deviation from the clinical investigation plan must be documented stating the explanation for the deviation, the date and any actions taken.

Significant deviations compromising or potentially compromising the safety of the subjects, enrolment of non-eligible subjects or any deviation, which significantly compromises the outcome of the study, must be reported to the ethics committee within the appropriate timelines indicated by the ethics committee.

8.7 Audit and supervision

Investigator sites and study documentation may be subject to quality assurance audits during the course of the study. In addition, regulatory bodies at their discretion may conduct inspections, during and after study completion.

8.8 Data and quality management

CRF data collected will be subject to data quality control measures in compliance with all applicable data management procedures. Edit checks will be applied to identify discrepant data. All CRFs will be audited against corresponding database output to ensure accuracy. Data management documentation will be generated and maintained throughout the process including the data management plan and associated project binders.

8.9 Safety committee

UNEEG™ medical will constitute an internal safety committee to perform ongoing safety surveillance.

8.10 Reporting of results

The results of the investigation will be summarised in a report to be used in the further development and approval of the device. The report will be forwarded to the ethics committee and competent authorities at the end of the investigation. The main findings of study will be submitted for publication in a peer reviewed journal or made public available www.clinicaltrials.gov.

8.11 Conflict of interest and financial support

The study is initiated by UNEEG™ medical and financed by UNEEG™ medical. The principal investigator is not affiliated with UNEEG™ medical and has full scientific integrity.

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