Title Page

Protocol Title:

A registry-based, open-label, randomized study to investigate quality-of-life with Plenadren compared with Cortison in participants aged 16-80 with newly diagnosed primary adrenal insufficiency

A registry-based prospective randomized unblinded parallel group clinical registry study designed to test if oral replacement treatment with Plenadren is superior to conventional oral treatment with Cortisone acetate in participants with newly diagnosed primary adrenal insufficiency. This is a Phase 4 study, and participants are assigned to one of two treatment types in parallel for the duration of the study. The primary outcome is improvement of health related quality-of-life.

Protocol Number: ADNorGC

Amendment Number: 5

Compound: Plenadren (hydrocortisone), Cortison (cortisone acetate)

Brief Title: Comparison of Plenadren and Cortsone in newly diagnosed primary adrenal insufficiency

Study Phase: 4

Acronym: CORTAD

Sponsor Name: Helse Bergen HF, Department of Medicine.

Legal Registered Address: Box 1400, N-5021 Bergen

Coordinating investigator: Prof. Eystein Husebye

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A registry-based, open-label, randomized study to investigate quality-of-life with Plenadren compared with Cortison in participants aged 16-80 with newly diagnosed primary adrenal insufficiency

EU CT No: 2021-006487-24

Sponsor Signatory:

Kahtan Al-Azawy Director of Department of Medicine	**Date**

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List of Abbreviations and Definitions of terms

AE, adverse event

BMD, bone mineral density

BDNF, brain-derived neurotrophic factor

CFR, Code for Federal Regulation

DSST, digital symbols substitution test

DXA, dual energy X-ray absorptiometry

HDL, high-density lipoprotein

ICH GCP, International Council for Harmonisation guidelines for Good Clinical Practice

ICF, International Classification of Functioning, Disability and Health

IDFU, investigational directions for use

IEC, Institutional Ethics Committee

IRB, Institutional Review Board

HRQoL, health-related quality of life

HUH, Haukeland University Hospital

LDL, low-density lipoprotein

PINP, N-terminal propeptide of type 1 procollagen

PAI, primary adrenal insufficiency

PVT, psychomotor vigilance test

RCT, randomized clinical trial

ROAS, The Norwegian National Addison Registry

ROI, region of interest

RRCT, registry-based randomized clinical trial

SAE, serious adverse event

SAT, subcutaneous adipose tissue

SOA, schedule of activities

SUSAR, suspected unexpected serious adverse reaction

VAT, visceral adipose tissue

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A registry-based, open-label, randomized study to investigate quality-of-life with Plenadren compared with Cortison in participants aged 16-80 years of age with newly diagnosed primary adrenal insufficiency

Objectives	Endpoints
Primary	
• Differences in health-related quality of life (HRQoL) scores in patients receiving Plenadren and conventional Cortisone at time of diagnosis and 1, 6, and 12 months	• HRQoL score
Secondary	
• Differences in clinical markers of cardio-metabolic health in patients receiving Plenadren and conventional thrice daily Cortisone at time of diagnosis and 6 and 12 months after treatment initiation.	• Blood pressure: systolic blood pressure and diastolic blood pressure • Body weight, waist circumference, and body mass index • Levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides • Levels of glucose, insulin, and HOMA index
• Differences in hair cortisol concentrations time of diagnosis and in patients receiving Plenadren and conventional Cortisone at 6 and 12 months after treatment initiation.	• Hair cortisol level
• Differences in salivary cortisol day curves in patients receiving Pleandren and conventional Cortisone at 6 and 12 months after treatment initiation.	• Salivary cortisol day curves

• Differences in the urinary cortisol metabolome in patients receiving Pleandren and conventional Cortisone at 6 and 12 months after treatment initiation.	• 24 h urine cortisol and metabolites
• Differences in sleep quality in patients receiving Plenadren and conventional Cortisone at 6-12 months after treatment initiation, using the following instruments:	• Sleep diary (https://helse-bergen.no/nasjonal-kompetansetjeneste-for-sovnsykdommer-sovno/sovndagbok-sovno) • Actigraphy • Sleep radar (somnofy)
• Differences in cognitive function in patients receiving Plenadren and conventional Cortisone at 1, 6 and 12 months after treatment initiation:	• Cognitive test administration using Memoro, a web-based cognitive test platform developed by Tor Ivar Hans and Asta Håberg, NTNU. • Biomarker for brain plasticity (BDNF) in serum
• Differences in bone metabolism and body composition receiving Plenadren and conventional Cortisone at 1, 6 and 12 months after treatment initiation:	• Bone mineral density (BMD) and Body composition Bone markers
• Differences in occurence of adverse events, registered during the study	• Adverse events • Serious adverse events • Register any adrenal crisis symptoms or treatment (separate form)

Brief Title:

Comparison of Plenadren and Cortsone in newly diagnosed primary adrenal insufficiency

Rationale:

The standard glucocorticoid replacement therapy has been largely unchanged since the 1950s, in Norway consisting of cortisone. An extended-release formulation of hydrocortisone marketed under the name Plenadren was approved for replacement therapy in 2011 and is currently used by about 20 percent of patients with PAI (1). Being an orphan drug, approval was based on an open study documenting reduction of weight, blood pressure, and glucose levels (2), and more recently, a beneficial effect on the urinary cortisol metabolome (3). Follow-up studies have confirmed that long-term use of Plenadren is safe, but superiority to conventional Cortisone has not been proven (4).

Objectives, Endpoints, and Estimands:

Overall design: Registry-based, open-label, single center, randomized, controlled academic investigational medicine study.

Brief Summary: The purpose of this study is to compare quality of life, metabolic parameter, bone health and sleep quality with Plenadren or Cortisone in patients with primary adrenal insufficiency.

Treatment duration: 12 months

Visit number and frequency: 6 visits

Number of Participants: 50

As we expect that most patients will agree to participate, approximately 60 participants will be screened to achieve 50 enrolled patients randomized to either Plenadren or standard Cortisone

Study Arms: Two, Plenadren or Cortisone

Data Monitoring/Other Committee: A monitor will be appointed to oversee conduct of the study according to the study specific monitoring plan provided by sponsor.

1.2. Schema

Potentially eligible study participants are all newly diagnosed patients with primary adrenal insufficiency (PAI). The diagnostic criteria are basal serum cortisol < 100 nmol/L combined with p-ACTH > 2 x upper reference limit: or synacthen—stimulated serum cortisol < 485 and p-ACTH > 2 x upper reference limit.

In patients randomized to conventional Cortisone, the initial replacement dosage will be 25 mg divided in three doses according to current clinical routine. Patients randomized to Plenadren will receive an initial dosage of 20 mg, as in previous clinical trials (17). One week after inclusion and treatment initiation, the patient will return for blood tests for evaluation and individual adjustment of the dosage.

The Section of Endocrinology at The Department of Medicine at Haukeland University Hospital (HUH) and The Endocrine Medicine Group at Department of Clinical Science at the University of Bergen (UiB) have built up a unit for translational research in endocrinology. The outpatient clinic is staffed with experienced personnel in handling patients and samples. The Fasttrack infrastructure to be used for registration of study information, is well established and used for all outpatient contacts at Section of endocrinology, Department of Medicine, Haukeland University Hospital. The system is available at all hospitals in Norway through Noklus Diabetes and can be used by the network of dedicated physicians. It has recently been used in clinical studies (27), and proven to be a safe, robust and efficient way to register study information. An array of autoantibody assays are available, including 21-hydroxylase autoantibodies. The core facility for

metabolomics at UiB is specialized in steroid metabolomics and can analyze steroids in blood, saliva, urine, and hair with ultrasensitive techniques.

Health-related quality of life will be assessed through a standard generic HRQoL questionnaire (SF-36) as well as the disease-specific HRQoL questionnaire (AddiQoL) to compare any effects of Plenadren and Cortisone on well-being and clinical functioning in patients with PAI. AddiQoL has been developed by our group and has been validated in multiple languages and is extensively used (21).

1.3. Schedule of Activities (SoA)

Procedure	Screening	Randomization	Intervention Period					End of study[1]
			Baseline	Phone visit	Lab visit			
Visit number	**1**		**2**	**3**	**4**	**5**	**6**	**7**
Days from baseline	**-31 to 0**		**0**	**7**	**28**	**182**	**365**	
Weeks from baseline			**0**	**1**	**4**	**26**	**52**	
Informed consent	X							
Inclusion and exclusion criteria	X							
Demography	X							
Pregnancy test	X							
Medical history (including menarche/menopause)	X							
Full physical examination including hip/waist, height and body weight, BMI, BP (sitting/standing) and pulse	X		X		X	X	X	
Randomization		X						
Submit prescription to pharmacy			X					
Patient education	X		X					
Register diagnosis in the summary care record (kjernejournal)	X		X					

Procedure	Screening	Randomization	Intervention Period					End of study[1]
			Baseline	Phone visit	Lab visit			
Visit number	**1**		**2**	**3**	**4**	**5**	**6**	**7**
Diagnostic laboratory tests adrenal insufficiency [1]	X							
Laboratory tests (hematology, electrolytes, creatine, liver enzymes, cholesterols and triglycerides, HbA1c, cobalamine, , ferritin, renin, aldosterone, 25OH vitamin D, TSH, FT4)			X			X	X	
HOMA index (insulin and glucose)			X			X	X	
Serum and EDTA samples for Biobanking forc-peptide, bone markers, BDNF, metylmalomic acid and autoantibody screening (etiology and autoimmune comorbidity)			X			X	X	
Urine sample (steroid metabolome)							X	
Hair sample (cortisol)			X				X	
HRQoL questionnaires (RAND-36, AddiQoL-30)			X		X	X	X	
Cognitive tests	X					X	X	
Bone mineral density and body composition					X		X	
Blood sampling 1 and 4 h after morning dose (S-cortisol)					X			
Dose adjustment according to S-cortisol (if applicable) [2]					X			
Saliva cortisol (before, +1h and +4 h after morning dose						X	X	

Procedure	Screening	Randomization	Intervention Period					End of study[1]
			Baseline	Phone visit	Lab visit			
Visit number	**1**		**2**	**3**	**4**	**5**	**6**	**7**
Review dosing and compliance				X		X	X	
Register the use of extra doses (oral or i.m./i.v.; for 4 weeks)						X	X	
Evaluation of sleep (Sleep diary, Actigraphy)						□==========□		
Working ability (sick leave, sick pension)			X				X	
Sleep radar (Somnofy)							X	
AE review			X	□==========□				X
SAE review			X	□==========□				X
Register any adrenal crisis symptoms or treatment (separate form)			X	□==========□				
Concomitant medication review			X	□==========□				
Noklus study form completion	X		X	X	X	X	X	X

[1] Register reason for screening failure, if applicable

[2] Diagnostic laboratory tests (21-OH-autoantibody, cortisol, ACTH, aldosterone, renin, cosyntropin stimulated cortisol if available)

2. Introduction

In primary adrenal insufficiency (PAI), the adrenal cortex is destroyed leading to a life-threatening lack of cortisol and aldosterone (5). The most common cause in Norway and other industrialized countries is autoimmunity. The disease most often affects young and middle-aged individuals and more women than men (6). The prevalence in Norway is among the highest in the world at 20 per 100 000 with an incidence of about 5 per million per year (1).

Before cortisone acetate became available in the late 1940-ies, PAI was invariably deadly (7, 8). Introduction of hydrocortisone and later fludrocortisone (to replace aldosterone) revolutionized treatment and converted PAI to a manageable disease with good prognosis. However, **even with best practice treatment, patients suffer** from reduced health-related quality of life (HRQoL), debilitating fatigue, and decreased physical activity (5, 9). The ability to tackle stress is reduced, and the rate of permanent sick pension is more than doubled (6). Both clinical and registry studies have shown increased risk of cardiovascular disease in PAI (10-12). More alarmingly, cardiovascular disease is considered a leading cause of the excessive death rates (10, 13, 14). PAI has also been associated with increased rates of infections (11) and reduced bone mineral density (15), either as a consequence of the disease itself or its treatment (16). The reasons for this ill-health is incompletely understood, but inability to mimic the circadian and ultradian rhythmicity of cortisol secretion is plausible (17).

The standard **replacement therapy has been largely unchanged since the 1950s**, although we and others have introduced new ways of administering glucocorticoids (e.g. by subcutaneous infusion) (18). An extended-release formulation of hydrocortisone marketed under the name Plenadren was approved for replacement therapy in 2011 and is currently used by about 20 percent of patients with PAI in Norway (1). Being an orphan drug, approval was based on an open study documenting reduction of weight, blood pressure, and glucose levels (2), and more recently, a beneficial effect on the urinary cortisol metabolome (3). Follow-up studies have confirmed that long-term use of Plenadren is safe, but superiority to conventional cortisone or hydrocortisone in randomized blinded trials has not been proven (4). Another factor is that a daily dose of Plenadren (NOK 130) costs almost 30 times that of Cortisone (NOK 4).

Despite the high-ranked position in the hierarchy of clinical evidence, double-blind randomized clinical trials (RCT) have limitations that need to be acknowledged, including prohibitive costs of adequately powered studies and strict inclusion criteria that limit the real-life applicability (19). In the setting of glucocorticoid replacement in PAI, a RCT is further hindered by the lack of a placebo medication for Plenadren, which is not available. Furthermore, the pharmaceutical industry has shown no interest to perform a double-blinded RCT trial that could challenge the current notion that Plenadren provides a better and more physiological replacement of glucocorticoids.

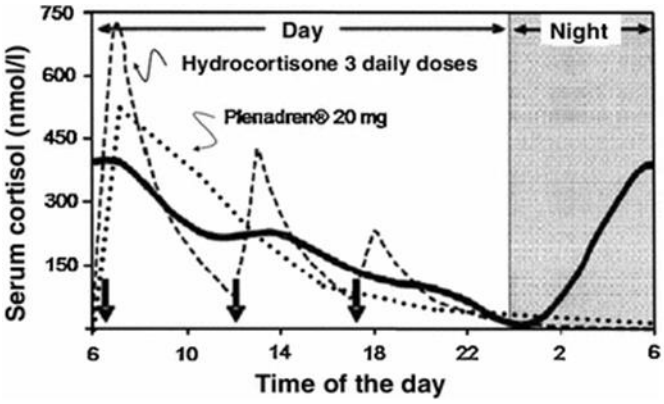
PAI is a rare, and clinical trials in recently diagnosed glucocorticoid-naïve patients non-existent but are needed to avoid the bias of previous patient treatment experience. Furthermore, long term national studies are required to achieve sufficient participant number. Recently, registry-based randomized clinical trials (RRCTs) have emerged as a new clinical trial paradigm to test treatment options, maintaining the advantages of traditional RCTs, but at a much lower cost and closer to real-life practice (19).

The National Addison Registry in Norway (ROAS) was founded in 1996 and has established itself as the largest of its kind in the world, covering about 65 percent of Norwegian patients with PAI (1). From 2012, it is also a medical quality registry, with quality assurance processes incorporated in the daily administration to ensure the integrity and quality of all registered data. The registry collects clinical information prospectively and stores biological samples in a biobank.

We are therefore in the unique position **to challenge previous open-labelled studies** and perform a prospective **RRCT** to **test if Plenadren is superior to standard therapy with Cortisone.**

2.1. Study Rationale

The study aims to identify the best current glucocorticoid replacement therapy in patients with PAI. There is a great need to determine the effect of the different treatment regimens, both on HRQoL, working ability, metabolic parameters such as weight, waist circumference, blood glucose, lipids, and blood pressure, frequencies of adrenal crises, and mortality rates. Some investigators claim that Plenadren is a more physiological treatment than thrice daily cortisone acetate or hydrocortisone (22-24), while others emphasize the importance of rhythmicity in glucocorticoid replacement, that to some degree is retained with thrice daily Cortisone. The current study can provide a clarification between the two modes of replacement. The ultimate goal is to be able to offer all patients the treatment option that best improves quality of life and working ability, protects against infections and adrenal crises as well as minimizing the long-term risk for cardiovascular and metabolic complications.



Schematic representation of serum cortisol levels after administration of either hydrocortisone thrice daily (dashed line) or an extended-release hydrocortisone preparation (Plenadren 20 mg) once daily (dotted line) compared with

The study will clearly fill a knowledge gap as it is currently not known if reported differences are based on differences in daily cortisol exposure or if differences are due to variations in steroid levels throughout the day. As cortisol is secreted in pulses with a frequency of 60-90 minutes, one could argue that the standard thrice daily regimen is more physiological than the treatment with an extended-release tablet where only one peak is reproduced (see figure). To avoid the potential bias of earlier studies due to their open design, we will only include newly diagnosed patients as these will be treatment-naïve and unable to compare with other forms of replacement therapy.

2.2. Background

As PAI infers lack of cortisol, patients depend on life-long glucocorticoid replacement therapy for survival. The standard treatment in Norway is oral Cortisone twice or thrice daily, which is converted to its bioactive counterpart hydrocortisone in the liver. Recently, modified release hydrocortisone, Plenadren, was designed for once daily replacement therapy in PAI. Both drugs are licensed for use in PAI and approved for use by the Norwegian Drug Agency. A detailed description of the chemistry, pharmacology, efficacy, and safety of Cortisone and Plenadren is provided in the respective summary of product characteristics (SmPC).

2.3. Benefit/Risk Assessment

Overall, we evaluate the participant risk as low, as both treatments are currently being used in PAI patients. More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of Plenadren and Cortisone may be found in the SmPC.

2.3.1. Risk Assessment

The risk is considered low since all the participants would be offered either one of these two therapies regardless of study participation. Both drugs are marketed and licensed in Norway for use as glucocorticoid replacement therapy in PAI. Both study drugs will be prescribed as for standard care, and thus will be stored, labeled and dispensed by a pharmacy. For the study participants study inclusion will imply a more extensive follow-up and more investigations, which can be perceived as a benefit or a minor inconvenience.

2.3.2. Benefit Assessment

The dosing will be adjusted to the patients' needs based on biochemical and clinical criteria. The potential risks identified in association with *treatment with Plenadren or Cortisone* are justified by the anticipated benefits that may be afforded to participants with *PAI.*

For the health service organization, the benefit is that the different treatment modalities will be compared in a scientifically sound way. Only then can one make recommendations and reimbursement systems that are cost-effective. It is important to have good evidence to defend the use of Plenadren that cost 30 times more than Cortisone per daily dose. If they show equal effectiveness and safety, the cheaper treatment is to be preferred in a health–economic perspective. Thus, the results can change clinical practice and reimbursement policies, not only in Norway, but also in other countries around the world where Plenadren is in use or being considered for use.

3. Objectives, Endpoints, and Estimands

The hypothesis to be tested is superiority of Plenadren compared to thrice daily Cortisone to improve patient outcome, including:

- Improved HRQoL, including mood and cognitive function
- Improved sleep quality
- Improved working ability (i.e. less sick leave, lower frequency of sick pension)
- Improved cognitive function
- Reduction in clinical risk factors of cardiovascular and metabolic diseases including weight, waist circumference, blood pressure, lipid profile, bone health, fat distribution and glucose levels.

Objective: To determine whether Plenadren or conventional Cortisone is superior for improving overall patient outcome in newly-diagnosed patients with PAI.

Primary endpoint: Differences in health-related quality of life (HRQoL) scores in patients receiving Plenadren and conventional Cortisone at time of diagnosis and 1, 6, and 12 months after treatment-initiation in newly diagnosed patients with PAI, using two validated questionnaires: one specific for PAI (AddiQoL-30) and one generic (RAND-36).

Secondary endpoints:

Evaluation of cardio-metabolic health:

- Differences in clinical markers of cardio-metabolic health in patients receiving Plenadren and conventional thrice daily Cortisone at time of diagnosis and 6 and 12 months after treatment initiation.
    - Blood pressure: systolic blood pressure and diastolic blood pressure
    - Body weight, waist circumference, and body mass index
    - Body composition, fat distribution
    - Levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides
    - Levels of glucose, insulin, and HOMA index

Evaluation of bone health:

- Differences in markers of bone health in patients receiving Plenadren and conventional Cortisone at time of diagnosis and 12 months after treatment initiation.
  - Vitamin D
  - N-terminal propeptide of type 1 procollagen (P1NP)
  - Bone mineral density (BMD) and Body composition

Evaluation of cortisol exposure:

- Differences in hair cortisol concentrations at time of diagnosis and 12 months after treatment initiation in patients receiving Plenadren and conventional Cortisone.
- Differences in salivary cortisol day curves in patients receiving Plenadren and conventional Cortisone at 6 and 12 months after treatment initiation.
- Differences in the urinary cortisol metabolome in patients receiving Plenadren and conventional Cortisone at 6 and 12 months after treatment initiation.

Evaluation of sleep:

- Differences in sleep quality in patients receiving Plenadren and conventional Cortisone at 6-12 months after treatment initiation, using the following instruments:
  - Sleep diary (https://helse-bergen.no/nasjonal-kompetansetjeneste-for-sovnsykdommer-sovno/sovndagbok-sovno)
  - Sleep radar and Actigraphy

Evaluation of cognitive function:

- Difference in reaction time and working memory in patients receiving Plenadren and conventional Cortisone at baseline and 6-12 months after treatment initiation, specifically targeting reaction time and working memory. Cognitive test administration using Memoro, a web-based cognitive test platform developed by Tor Ivar Hans and Asta Håberg, NTNU (28-30).

Evaluation of safety:

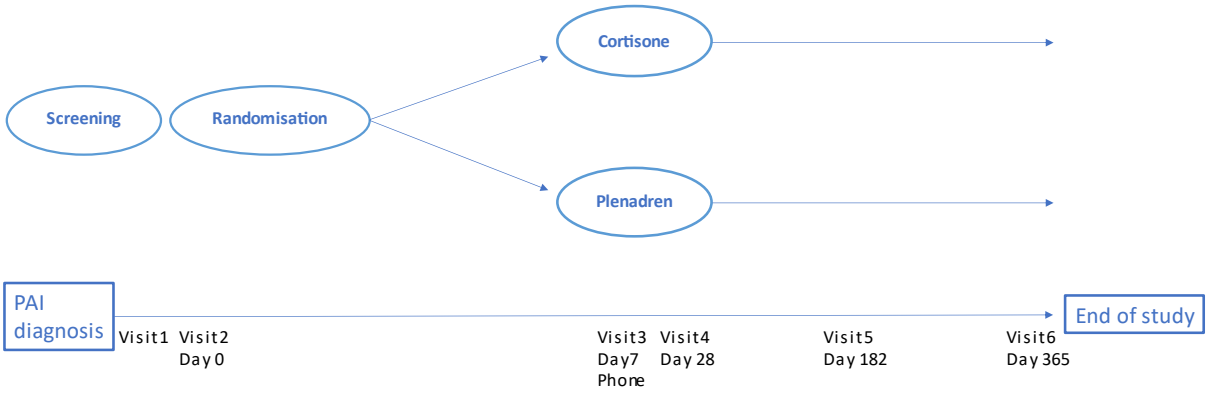
- Differences in occurrence of adverse events, registered during the study
  - Adverse events
  - Serious adverse events
  - Register any adrenal crisis symptoms or treatment (separate form)

Objectives	Endpoints
Primary	
• Differences in health-related quality of life (HRQoL) scores in patients receiving Plenadren and conventional Cortisone at time of diagnosis and 1, 6, and 12 months	• HRQoL score
Secondary	
• Differences in clinical markers of cardio-metabolic health in patients receiving Plenadren and conventional thrice daily Cortisone at time of diagnosis and 6 and 12 months after treatment initiation.	• Blood pressure: systolic blood pressure and diastolic blood pressure • Body weight, waist circumference, and body mass index • Levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides • Levels of glucose, insulin, and HOMA index
• Differences in hair cortisol concentrations time of diagnosis and in patients receiving Plenadren and conventional Cortisone at 6 and 12 months after treatment initiation.	• Hair cortisol level
• Differences in salivary cortisol day curves in patients receiving Plenadren and conventional Cortisone at 6 and 12 months after treatment initiation.	• Salivary cortisol day curves
• Differences in the urinary cortisol metabolome in patients receiving Pleandren and conventional Cortisone at 6 and 12 months after treatment initiation.	• 24 h urine cortisol and metabolites
• Differences in sleep quality in patients receiving Plenadren and conventional Cortisone at 6-12 months after treatment initiation, using the following instruments:	• Sleep diary (https://helse-bergen.no/nasjonal-kompetansetjeneste-for-sovnsykdommer-sovno/sovndagbok-sovno) • Actigraphy • Sleep radar (Somnofy)

Objectives	Endpoints
• Differences in cognitive function in patients receiving Plenadren and conventional Cortisone at 1, 6 and 12 months after treatment initiation:	• Reaction time, working memory and verbal learning and memory • Cognitive test administration using Memoro, a web-based cognitive test platform developed by Tor Ivar Hans and Asta Håberg, NTNU. • Biomarker for brain plasticity (BDNF)
• Differences in bone metabolism and body composition receiving Plenadren and conventional Cortisone at 1, 6 and 12 months after treatment initiation:	• Bone mineral density (BMD) and Body composition • Bone markers
• Differences in occurence of adverse events, registrated during the study	• Adverse events • Serious adverse events
• Differences in occurence of adverse events, registered during the study	• Adverse events • Serious adverse events • Register any adrenal crisis symptoms or treatment (separate form)

4. Study Design

4.1. Overall Design



This is a phase 4 RRCT designed to test if oral replacement treatment with Plenadren is superior to conventional oral treatment with Cortisone in participants with newly diagnosed PAI between 16-80 years of age. The participants are assigned to one of two treatment types in parallel for the duration of the study. The primary outcome is improvement of HRQoL. To avoid the potential bias we will only include newly diagnosed patients as these will be treatment-naïve and unable to compare with other forms of replacement therapy.

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit.

4.2. Scientific Rationale for Study Design

4.2.1. Choice of study design

The standard glucocorticoid replacement therapy has been largely unchanged since the 1950s, in Norway consisting of cortisone. An extended-release formulation of hydrocortisone marketed under the name Plenadren was approved for replacement therapy in 2011 and is currently used by about 20 percent of patients with PAI in Norway (3). Being an orphan drug, approval was based on an open study documenting reduction of weight, blood pressure, and glucose levels (17), and more recently, a beneficial effect on the urinary cortisol metabolome (18). Follow-up studies have confirmed that long-term use of Plenadren is safe, but superiority to conventional

Cortisone has not been proven (19). Another factor is that a daily dose of Plenadren (NOK 130) costs almost 30 times that of Cortisone (NOK 4).

Despite the high-ranked position in the hierarchy of clinical evidence, double-blind RCTs have limitations that need to be acknowledged, including prohibitive costs of adequately powered studies and strict inclusion criteria that limit the real-life applicability (19). In the setting of glucocorticoid replacement in PAI, a RCT is further hindered by the lack of a placebo medication for Plenadren, which is not available. Furthermore, the pharmaceutical industry has shown no interest to perform a double-blinded RCT trial that could challenge the current notion that Plenadren provides a better and more physiological replacement of glucocorticoids.

PAI is a rare, and clinical trials in recently diagnosed glucocorticoid-naïve patients non-existent but are needed to avoid the bias of previous patient treatment experience. Furthermore, long term national studies are required to achieve sufficient participant number. Recently, RRCTs have emerged as a new clinical trial paradigm to test treatment options, maintaining the advantages of traditional RCTs, but at a much lower cost and closer to real-life practice (19).

4.2.2. Patient Input into Design

Patient representative Kari Hystad has been part of the study group from the planning stage and have given valuable input into the protocol and consent form, e.g. clarifying the text and making it more understandable. The patient organization have a particular interest in studies of fatigue in PAI, and fatigue, a component of HRQoL is a main focus of the study. They are also very focused on diversity and availability of drugs for replacement therapy and the current study aligns well with the Morbus Addison Association of Norway's goals.

The patient representative have read and provided input to the protocol and the consent form, mainly to clarify the text and make it more understandable

4.3. Justification for glucocorticoid dose

In patients randomized to conventional Cortisone, the initial replacement dosage will be 25 mg per day according to current clinical routine. Patients randomized to Plenadren will receive an initial dosage of 20 mg, as in previous clinical trials (17). One week after inclusion and treatment initiation, the patient will return for blood tests for evaluation and individual adjustment of the dosage. No study-specific dose increase or dose reduction protocols apply. Participant dosage is titrated by the participants' endocrinologist if needed using a structured symptom history (Pearce's questions form). Cortisol measurement at 1 and 4 hours after morning dose is measured to detect gross overdosing or lack of absorption of drug. Saliva cortisol is sampled at 1 and 4 hours after morning dose at 6 and 12 months.

5. Study Population

Potentially eligible study participants are all newly diagnosed patients in Norway with PAI independent of etiology. The diagnostic criteria are basal serum cortisol < 100 nmol/L combined with p-ACTH > 2 x upper reference limit; or co-syntropin stimulated serum cortisol < 485 nmol/L and p-ACTH > 2 x upper reference limit (29).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Age between 16-80 years.
2. Established PAI according to the diagnostic criteria as specified above.
3. Participants must be recently diagnosed, specifically treated with glucocorticoid replacement therapy for less than 31 days prior to inclusion to secure treatment naivety.
4. Women of childbearing potential (WOCBP)* must have a negative pregnancy test performed at the time of screening.
5. Participants must be capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

** For the purpose of this study, a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.*

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

1. Ongoing treatment for active malignant disease
2. Severe hepatic or renal disease
3. Sever psychiatric disease
4. Chronic abuse of alcohol or drug abuse
5. Current pregnancy, and if the participant plan to become pregnant during the 12 months of study participation.
6. Known hypersensitivity to the active substance or any of the excipients.

Prior/Concomitant Therapy

7. High dose glucocorticoid therapy for other disease during last three months prior to screening. This includes steroid injections for allergic disease and injections into joints. Local glucocorticoid treatment (inhalations, nasal spray or creams for use on skin) is allowed.

Prior/Concurrent Clinical Study Experience

8. Participation in another blinded clinical study involving an investigational medicinal product within 1 month prior to study inclusion

Diagnostic Assessments

9. Participants not fulfilling the diagnostic criteria for PAI, as specified above in 5.1.

Other Exclusion Criteria

10. Not applicable

5.3. Lifestyle Considerations

There are no lifestyle restrictions for study inclusion.

5.3.1. Other Restrictions

There are no other restrictions for study inclusion.

5.4. Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned to study intervention and entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

6. Study Intervention(s) and Concomitant Therapy

6.1. Study Intervention(s) Administered

Participants will be randomized to replacement therapy with either Cortisone or Plenadren for the duration of the study. Starting dose for Cortisone is thrice daily (12.5 mg morning, and 6.25 mg at noon and 6.25 mg in the afternoon). Starting dose for Plenadren is once daily 20 mg (morning). Both investigational drugs have marketing authorization and will be prescribed by the patients treating endocrinologist as for patients not included in the study. Thus, there are no study specific drug labelling or packaging.

Since all participants are newly diagnosed with PAI, treatment with fludrocortisone is also required from time of diagnosis as per standard care. Concomitant fludrocortisone treatment will not be a subject of any study specific restrictions.

Table 6.1. Study Intervention(s) Administered

Intervention Label	Cortison	Plenadren
Intervention Name	Cortison	Plenadren
Intervention Description	Oral, TID	Oral, OD
Type	Cortisone acetate	Hydrocortisone
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	25mg	20mg
Dosage Level(s)	12.5mg +6.25mg+6.25mg	20mg OD
Route of Administration	Oral	Oral
Use	Active comparator	Test
IMP and NIMP/AxMP.	IMP	IMP
Sourcing	Provided by the pharmacy per prescription as per standard care	Provided by the pharmacy per prescription as per standard care
Packaging and Labeling	Not applicable	Not applicable

Table 6.2. Study Arm(s)

Arm Title	Cortison	Plenadren
Arm Type	Active comparator	Test

6.2. Preparation, Handling, Storage, and Accountability

Both Plenadren and Cortison are provided by the pharmacy per prescription as standard care. The medication is stored and handled according to the pharmacy's procedure. There will be no drug inventory accountability since the drug is taken form the pharmacy's storage.

6.3. Assignment to Study Intervention

This study will be using randomization, performed in blocks of four and performed at the central study site at HUH. The study investigators will contact HUH by calling a dedicated phone number. A study nurse will assign treatment type.

6.4. Blinding, Masking

This is an open-label study; potential bias will be reduced by central randomization.

6.5. Study Intervention Compliance

Participants self-administer study intervention(s) at home, and compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of Cortison or Plenadren dispensed by the pharmacy to the participants and administered by each participant is available in the core record (kjernejournal),

6.6. Dose Modification

Participants will start on either 20 mg Plenadren once daily or 25 mg Cortisone divided in three daily doses. The Cortisone tablet can be divided into halves or quarters so that one half is given in the morning, a quarter at midday and a quarter in the afternoon (12.5 + 6.25 + 6.25 mg daily). Any dose modification can be made at the discretion of the study investigators. The study protocol includes measurement and cortisol in saliva and serum to aid clinicians in dose modification. Likewise we have developed ten clinical questions for the patients to clarify symptoms that may indicate a need for dose adjustment.

After one week serum cortisol will be sampled one and four hours after ingesting the morning dose to assess drug uptake. If a dose change is deemed necessary based on these results and clinical evaluation of the patient, the doses will be altered if necessary, and documented in the study files. If the patient develops symptoms and/or signs of overtreatment with glucocorticoid (unexpected weight gain, Cushingoid clinical signs), a dose reduction will be instituted at the investigators discretion, normally a 25% reduction in daily dose. Accordingly, if the patient has symptoms of undertreatment (i.e. debilitating fatigue, increased pigmentation) and post dose serum cortisol levels are low, a dose increase will be instituted at the investigators discretion, normally a 25% increase in daily dose.

6.7. Continued Access to Study Intervention after the End of the Study

The patient will continue on Cortisone treatment after the study with the option to start or continue with Plenadren at the investigators discretion.

6.8. Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study, must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

6.8.1. Rescue Medicine

The study site will not supply any form of study specific rescue medication. However, participants will be prescribed hydrocortisone for intramuscular use as per standard care, for use in case of an adrenal crisis. Occurrence of adrenal crisis will be documented at each study visit in the study-specific form. An adrenal crisis leading to admission will be registered as a SAE.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Replacement therapy with either Plenadren or Cortisone is needed at all times. If a participant experience side-effects that might be related to ingredients in the tablet or do not obtain sufficient effect, other means of glucocorticoid replacement must be considered at the discretion of the investigator.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the investigator for safety reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study intervention and the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits or is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (for time line se figure on page 22). eCRF forms are generated using the Fasttrack infrastructure and is available in Endojournal and Noklus Diabetes at every hospital, one form per visit (visits 1-6). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (ie, hormone levels at diagnosis, 21-OH autoantibodies, blood count, renal function, glucose, electrolytes, lipids) obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Administrative Procedures

8.1.1. Screening visit (Visit 1)

No study related procedures must be performed before the patient has been informed about the study and the informed consent form is signed and dated by both the patient and the investigator, according to procedure described in section 10.1.3.

Exceptions: procedures conducted as part of the participant's routine clinical management (ie, hormone levels at diagnosis, 21-OH autoantibodies, blood count, renal function, glucose, electrolytes, lipids) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the timeframe defined in the SoA.

For simplification, tasks for the recruiting physician at visits 1 and 2 are summarized below:

Screening, Inclusion and Randomisation (tasks for the recruiting physician)

- Provide information and ensure signed informed consent (stored on paper).
- Fill inn study form in Noklus diabetes (Fasttrack).
- Etiology of PAI: Determine 21-hydroxylase autoantibodies to secure diagnosis of autoimmune PAI. In antibody-negative patients: a computer tomography of the adrenal region is required to look for tumour, bleeding, or infections, or known bilateral adrenalectomy.
- Regular blood chemistry including hemoglobin, erythrocyte volume fraction, leucocytes, thrombocytes, creatinine, Na, K, calcium, magnesium, and alanine amino transferase and lipids (if not already done).
- Screening for common endocrine co-morbidities is performed:
  - Autoimmune thyroid disease: TSH, FT4, anti-thyroperoxidase, anti TSH-receptor autoantibodies.
  - Autoimmune gastritis: cobalamin, ferritin, methyl malonic acid, parietal cell antibodies and intrinsic factor autoantibodies.
  - Type 1 diabetes: HbA1c.
  - Celiac disease: transglutaminase-2 autoantibodies.
- Serum, EDTA blood (DNA), urine (steroid metabolome), and hair sample (cortisol) for biobanking
- Clinical examination including, height, weight, waist circumference, blood pressure (standard protocol) sitting and standing. Please note pigmentation, signs of vitiligo or alopecia, menstruation (menarche, menopause) in women.
- HRQoL questionnaires (AddiQoL and RAND-36)
- Randomization to either Cortisone or Plenadren.
- Education in stress dosing, sick-day rules, self-injection of hydrocortisone, and issuing of steroid card.
- Submit prescription to pharmacy.
- Register diagnosis in the summary care record (“Kjernejournal”).
- Schedule blood sampling 1 and 4 hours after intake of GC replacement morning dose for evaluation and adjusting of the dosage at Visit 3.
- Cognitive testing

8.1.2. Randomization and Baseline visit (Visit 2)

Randomization to either Cortisone or Plenadren can be done after screening and attaining an informed consent, either before or at visit 2 (day 0). The including investigator will the study nurse at HUH on a dedicated phone number and the consenting participant will be randomized to either treatment type. Randomization will be performed centrally and in blocks of four to secure equal assignment number in each group. A prescription for the study drug including recommended dosage will thereafter be provided to the patient.

8.1.3. Follow-up visits

Visit 3 – Telephone visit 1 week after inclusion

- Physician/ nurse: Interview the patient on the effect of the medication by filling out the adrenal insufficiency form in Noklus Diabetes.

Visit 4 - 1 month

- Physician/ nurse: Interview the patient on the effect of the medication by filling out the adrenal insufficiency form in Noklus Diabetes.
- Patient: Fill in PROMS, including HRQoL questionnaires.
- Note any side-effects, adrenal crisis, infections, or any new concomitant disease and their treatment.
- Blood sampling is performed for serum cortisol 1 and 4 hours after intake of GC replacement morning dose for evaluation and adjusting of the dosage.
- Bone mineral density measurement, body composition, and measure bone markers as well as vitamin D.

Visits 5 and 6 – 6 and 12 months (tasks for the recruiting physician)

- Physician/ nurse: Interview the patient on the effect of the medication by filling out the adrenal insufficiency form in Noklus Diabetes. Review dosing/ compliance, extra doses, side-effects, use of self-injection, and adrenal crises management.
- Regular blood chemistry including hemoglobin, Erythrocyte volume fraction, leucocytes, thrombocytes, creatinine, Na, K, calcium, magnesium, alanine amino transferase.
- Biobanking: serum and EDTA, urine, saliva (0,1 and 4 hours after morning dose), and hair examples.
- Patient: PROMS, including HRQoL questionnaires. At visit 5 or 6: Sleep diary actipragphy and sleep radar.

- At visit 6: Bone mineral density measurement, body composition, and measure bone markers as well as vitamin D.

8.2. Efficacy Assessments

Planned timepoints for all assessments are provided in the SoA.

8.2.1. Patient Reported Outcome (PROMs)

- Two HRQoL will be sampled at baseline and after 1, 6 and 12 months; the generic questionnaire RAND-36 and the PAI-specific questionnaire AddiQoL. RAND-36 is thoroughly validated and extensively used and suitable both for comparison of HRQoL scores between PAI and healthy controls, and for comparing score between PAI and other disease groups (20). The AddiQoL is developed and thoroughly validated by us as a PAI-specific HRQoL instrument, more sensitive for detecting changes in HRQoL over time in PAI (21).
- For evaluation of sleep, Sleep Diary will be sampled at visit 5-6.
- Working ability (i.e. sick leave, sick pension) will be registered at each visit (NOKLUS study form).
- Cognitive test administration using Memoro, a web-based cognitive test platform developed by Tor Ivar Hans and Asta Håberg, NTNU (28-30). The test can be run on a computer, tablet, or smartphone. Participants receive links via sms, e-mail, as a printed pdf (letter) or through helsenorge.no. Memoro uses same encryption as online banking (nettbanken) and has ROS analysis approving the system. The server is located at NTNU's central server location. No clinical data is stored only the test scores. Some background variables are stored to provide norm data for references (year born, education level according to groups (vgs., bachelor, master or above) and handedness). Participants can receive their scores relative to the norm data if that is of interest. Score will be transferred directly to TSD or similar server at UiT/Haukeland or via encrypted file sender. The cognitive tests that will be used have been used in many other studies (incl. HUNT and MoBa) and have therefore system norms as a reference.

8.2.2. Body measures

Body weight, height and waist circumference should be measured as follows;

- Weight is registered after bladder voiding
- Shoes and coat/jacket should be taken off
- Pockets should be emptied of heavy objects (i.e. keys, coins, etc)

8.2.3. Blood sampling

Table 8.2.3 Laboratory parameters (blood, serum, plasma)	
Hematology	
• Hemoglobin • WBC/leukocytes	• Platelet count / thrombocytes
Lipids	
• Cholesterol • HDL	• LDL • Triglycerides
Clinical chemistry	
• HbA1c • Glucose • Creatinine • Ferritin	• Potassium • Sodium • Cobalamin • P1NP • 25OH Vitamin D
Hormones	
• TSH (thyroid stimulating hormone) • Free T4 • TPO antibodies • Cortisol • ACTH • DHEAS	• Aldosterone • Renin • Insulin • Insulin C-peptide • 21OH antibody

8.2.4. Saliva sampling

Saliva day curve for analysis of cortisol and cortisone, sampled at time 0, 1 and 4 hours after morning dose.

8.2.5. Urine sampling

Urine will be sampled for 24 h for analysis of urine cortisol and metabolites (LCMSMS) at visit 5 and 6. Sampling will start early morning with an empty bladder and continue collecting to include the first void the next morning. The participant will measure and register the 24 h urine volume and bring a small sample (10 mL) for analysis.

8.2.6. Hair sampling

Hair sampling will be performed at visit 6. We will collect scalp hair samples in AAD patients and healthy controls at one time point. The sampling will be done in concordance with the procedure described by Wester and Van Rossum (2015). First, will separate a lock of hair as thick as a pencil at the posterior vertex of the head. Using a scissor, the lock will as close to the scalp as possible. The proximal three cm of hair will be taped to a paper card with a line marking the proximal end of the sample. Hair samples shorter than three centimeters will be excluded from analysis. In patients with thin hair, we will ensure

a cosmetically satisfactory result by collecting two hair locks from two parallel positions of the posterior vertex and joining them together on the paper card. We will note information on when the hair was last washed, hair color, if the hair has been dyed the last three months, use of any hair product at the time of sampling, and patient ethnicity. The hair sample cards were stored in an envelope at room temperature until analysis.

Samples will be placed in a glass vial, labelled, and weighed individually. Samples should weigh close to 10 mg, but samples down to 2.5 mg will be included (Noppe et al, 2015). Then, samples will be cut in 1 cm length and washed in 2 ml LC-MS grade isopropanol at room temperature before left to dry for at least two days. Next, we will transfer the samples to a glass tube for mincing. Following this, we will add 1.4 ml methanol and 100 µl internal standards before incubation at 25 °C for 18 hours. Subsequently, samples are to be centrifuged at 4500 rpm, 4 °C for 5 minutes. One ml of clear supernatant will be transferred into a new glass tube and placed under a constant stream of nitrogen gas at 50 °C for drying.

Afterwards, we will add 1 ml 2% methanol and vortexed for 1 minute. Next, samples will be cleaned by solid-phase extraction using Oasis HLB 30 µl 96-well extraction plates on a 96-well positive pressure manifold, conditioned with 1 ml of methanol followed by 1 ml Milli-Q. Then, samples will be loaded with 1 ml of resuspended extract, washed with 1 ml 30% LC-grade methanol in Mili-Q, and eluted twice with 300µl methanol. Finally, samples are again placed under a constant stream of nitrogen gas at 50 °C for drying. Before analysis samples will be stored at 4 °C.

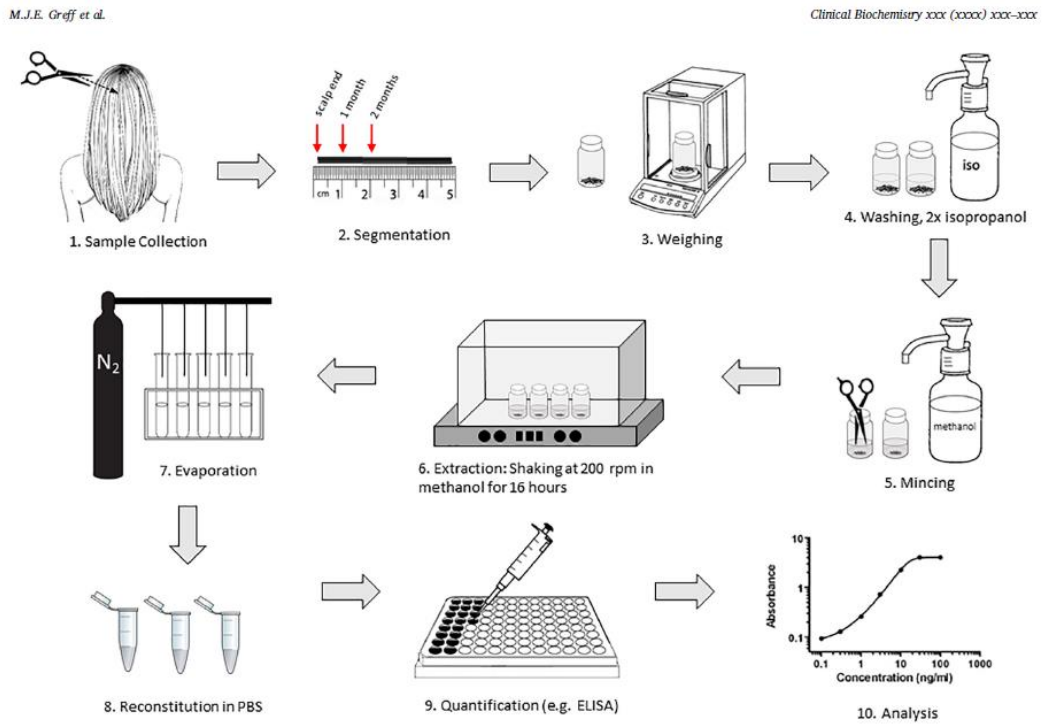


Fig. 1. Standard method for the quantification of hair cortisol concentration.

8.2.7. Bone mineral density and Body composition

Dual-energy x-ray absorptiometry (DXA), GE Healthcare Lunar Prodigy densitometer will be used to measure bone mineral density (BMD) in the lumbar spine (LS) L1-L4, total hip and body composition. The scans were analysed using enCORE software version 17 (SP4) (GE Healthcare). No hardware changes were made during the study period. Calibration will be performed daily using a calibration block consisting of tissue-equivalent material with three bone-simulating chambers, as supplied by the manufacturer (1). Standard imaging and positioning protocols will be used to scan the subjects. All scans will be performed by certified densitometry technologists. In vivo short-term coefficients of variation for total body tissue and lean and fat mass are 0.1%, 0.8%, and 2.5% (2). The VAT short-term repeat measurement error coefficient of variation is 9.8% (3).

For measuring android fat, a region of interest (ROI) is defined with the caudal limit at the top of the iliac crest and the cephalic limit at the base of the skull. The height of the android ROI will be automatically set to 20% of the distance from the iliac crest to the base of the skull. Android ROI contains both visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). The software estimates the quantity of SAT in the android ROI. VAT was computed by subtracting SAT from the total android fat. The fat

mass data from DXA was transformed to volume using a constant correction factor (0.94g/cm3) consistent with the density of adipose tissue (4).

8.2.8. Sleep

Evaluation of sleep will be performed for one week in between visit 5 and 6:

Actiwatch Spectrum (Philips), a watch-like accelerometer and photodiode sensor placed on the wrist, will continuously provide information about motor activity, sleep (sleep timing and efficiency), and light exposure (white and colored light) during the experimental protocol. Data can be converted to objective sleep parameters (25)

Sleep radar: Sleep quality will be assessed by a newly developed Norwegian Sleep Radar based on radio ultra wideband pulse-doppler radar technology enables long-term non-invasive sleep recording (Somnofy, Vital Things AS). The sleep algorithm has been validated to provide sleep stage classification with a precision close to what can be achieved using brain activity monitoring using deep neural networks machine learning (26).
Sleep diary: SurveyXact will be used in consultation with sleep researchers in University of Bergen.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.3.1. Vital Signs

Pulse rate, pulse quality and blood pressure will be recorded, both sitting and standing, with a completely automated device. Manual techniques will be used only if an automated device is not available.

- Blood pressure and pulse measurements should be preceded by at least five minutes of rest for the participant in a quiet setting without distractions (e.g. television, cell phones).
- For blood pressure measurements, two consecutive blood pressure readings will be recorded at intervals of at least one minute. The lowest of the two blood pressure readings will be recorded. After one minute standing a measurement will be performed.

8.3.2. Electrocardiograms

Not applicable.

8.3.3. Clinical Safety Laboratory Tests

- See the SoA (Section 1.3) for the timing and frequency of laboratory tests.

- To assess dose safety, serum cortisol will be measured 1 and 4 hours after the participant has administered the morning dose between visit 2 and 3. If a dose increase or decrease is deemed necessary, cortisol measurement 1 and 4 hours after the participant has administered the morning dose will be repeated after one week.

Table 8.3.3. Laboratory parameters for PAI diagnosis at screening (blood, serum, plasma)	
Hematology	
• Hemoglobin • WBC/leukocytes	• Platelet count / thrombocytes
Lipids	
• Cholesterol • HDL	• LDL • Triglycerides
Clinical chemistry	
• HbA1c • Glucose • Creatinine • Ferritin	• Potassium • Sodium • Calcium • Albumin • Cobalamin
Hormones	
• TSH (thyroid stimulating hormone) • Free T4 • TPO antibodies • 21-OH antibodies	• Renin • Aldosterone • Cortisol • ACTH • DHEAS

- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- [If clinically significant/any] values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
- All protocol-required laboratory tests must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.3.4. Pregnancy Testing

Pregnancy testing should be done if menstruation stops or becomes irregular. If pregnancy is confirmed, the participant should be withdrawn from the study.

8.3.5. Suicidal Ideation and Behavior Risk Monitoring

Glucocorticoids in replacement doses are not considered to be a CNS-active intervention.

8.4. Adverse Events (AEs) Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix [3/7].

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7). This includes events reported by the participant.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix [3/7].

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs and AEs will be collected from the start of study intervention until visit 6 at the time points specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix [3/7]. The investigator will submit any **updated SAE data to the sponsor within 24 hours** of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the

event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator Brochure (IB) investigational directions for use (IDFU) or state other documents] and will notify the Institutional Review Board (IRB) and Institutional Ethics Committee (IEC), if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4.5. Pregnancy

- Pregnancy at screening and planned pregnancy during the duration of study participation is an exclusion criteria. However, all AD patients (including all study participants) need to continue using one of the study drugs throughout the pregnancy as cortisol is a hormone necessary for survival in this patient group. The two study drugs in this study are the only approved treatment options in Norway. Therefore,

study participants who become pregnant during this trial will not be discontinued from study treatment.

- Pregnant AD patients may need alterations of doses which will be performed by local study investigators independently of study participation.
- If a pregnancy is reported during the study, the investigator will record pregnancy information in the appropriate form and submit it to the sponsor.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

8.5. Pharmacokinetics

Serum/saliva/urine/hair samples will be collected for measurement of cortisol and metabolites as specified in the SoA (Section 1.3)

8.6. Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

- 21-hydroxylase autoantibodies are assayed to diagnose the etiology of primary adrenal insufficiency.
- TPO antibodies are assayed to diagnose any thyroid comorbidity in PAI patients.
- Biomarkers of cardiovascular health and bone health are given in the protocol.

  BDNF, biomarker of brain plasticity in serum

8.9. Immunogenicity Assessments

Immunogenicity to the study drugs is not a clinical problem

9. Statistical Considerations

The statistical analysis plan will be finalized prior to inclusion of the first participant and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1. Statistical Hypotheses

Table 4 includes all objectives with corresponding hypothesis and statistical analyses.

Number	Objective	Hypotheses	Statistical analysis
	Primary		
1.1	Is improvement of HRQoL in PAI patients treated with Plenadren better than improvement of HRQoL in PAI patients treated with Cortisone after 6 and 12 months?	Null hypothesis: H_0: $P_{Plen(0-12)} = P_{Cort(0-12)}$ Alternative hypothesis: H_1: $P_{Plen0-12} \neq P_{Cort0-12}$ $P_{Plen\ (0-12)}$: Increase in HRQoL score from Baseline to 6 and 12 months in Plenadren-treated patients $P_{Cort(0-12)}$: Increase in HRQoL score from Baseline to 6 and 12 months in Cortison-treated patients	Between group comparison of longitudinal change in HRQoL score by linear mixed effect models for repeated measures.
	Secondary		
2.1	Is there a between group difference in clinical markers of cardio-metabolic health between patients receiving Plenadren and conventional thrice daily Cortisone for 12 months?	Null hypotheses: There is no difference in clinical markers of cardio-metabolic health between patients receiving Plenadren and	Comparing between-group clinical characteristics (BP, BW, BWC, BMI), lipids, glucose and HOMA index between Plenadren-treated and Cortison-treated patients.

		patients receiving Cortisone	Statistical analysis of paired non-parametric data; i.e. Mann-Whitney U test.
2.2	Is there a difference in hair cortisol concentration in patients receiving Pleandren compared to patients receiving Cortisone at 12 months after treatment initiation?	Null hypotheses: There is no difference in hair cortisol concentration between patients receiving Plenadren and patients receiving Cortisone	Statistical analysis of paired non-parametric data; i.e. Mann-Whitney U test.
2.3	Is there a difference in salivary cortisol day curves in patients receiving Plenadren and conventional Cortisone at 12 months after treatment initiation?	Null hypothesis: There is no between-group difference in salivary cortisol AUC	Statistical analysis of paired non-parametric data; i.e. Mann-Whitney U test.
2.4	Is there a difference in the urinary cortisol metabolome in patients receiving Plenadren compared to patients receiving Cortisone at 12 months after treatment initiation?	Null hypothesis: There is no between-group difference in urine cortisol metabolome	Statistical analysis of paired non-parametric data; i.e. Mann-Whitney U test.
2.5	Is there a difference in change of sleep score in patients receiving Plenadren and patients receiving Cortisone 6 and 12 months after treatment initiation	Null hypothesis: There is no between-group difference in changes of sleep score from baseline to 6 and 12 months of treatment	Between group comparison of longitudinal change in sleep score by linear mixed effect models for repeated measures.
2.6	Is there a difference in sleep quality between patients receiving Plenadren and patients receiving Cortisone at 12 months?	Null hypothesis: There is no between-group difference in sleep quality	Statistical analysis of paired non-parametric data; i.e. Mann-Whitney U test
2.7	Is there a difference in cognitive function in patients receiving Plenadren and	Null hypothesis: H_0: $P_{Plen(0-12)} = P_{Cort(0-12)}$	Between group comparison of longitudinal change in cognitive test

	patients receiving Cortisone at 1, 6 and 12 months after treatment initiation?	Alternative hypothesis: H_1: $P_{Plen0\text{-}12} \neq P_{Cort0\text{-}12}$ $P_{Plen\ (0\text{-}12)}$: Increase in cognitive test scores from Baseline to 6 and 12 months in Plenadren-treated patients $P_{Cort(0\text{-}12)}$: Increase in cognitive test scores from Baseline to 6 and 12 months in Cortison-treated patients	scores by linear mixed effect models for repeated measures
2.8	Is there a difference in change of bone markers in patients receiving Plenadren and patients receiving Cortisone 6 and 12 months after treatment initiation	Null hypothesis: There is no between-group difference in changes of bone markers from baseline to 6 and 12 months of treatment	Between group comparison of longitudinal change bone markers by linear mixed effect models for repeated measures
2.9	BMD/Body composition	Null hypothesis: There is no between-group difference in changes of bone mineral density and body composition from baseline to 12 months of treatment	Between group comparison of longitudinal change in bone mineral density and body composition by linear mixed effect models for repeated measures

9.1.1. Multiplicity Adjustment

Not applicable.

9.2. Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to end of trial and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

The main statistical analysis is planned when

- The planned number of participants have been included
- All included participants have either finalized their last assessment or has/is withdrawn according to protocol procedures
- All data have been entered, verified and validated according to the data management plan

9.2.1. General Considerations

Descriptive statistics will be presented with number and percentages for categorical variables and means and standard deviation for continuous variables. In case of clearly skewed continuous variables, they will be presented with median and interquartile range (25th and 75th percentiles). Demographics and baseline characteristics will be presented with descriptive statistics without any hypothesis testing. Continuous variables will be analyzed by t-tests, linear regression, mixed models or appropriate non-parametric alternatives. To investigate a treatment-by-time effect on relevant variables, we will use the likelihood ratio test by comparing the log-likelihood between models with and without the treatment-by-time term. To obtain P for trend in means within treatment groups, the effect of time will be included as a linear term in the mixed effect model, using the z test. To obtain P for model-predicted mean difference between treatment groups for different visit time, we will perform a post-hoc test for pairwise comparison (z test).

If missing data is regarded as having a significant effect on the conclusions of the trial, sensitivity analyses with different methods for handling missing data will be included. Such methods may include complete case analyses, worst case/best case imputation and multiple imputation techniques.

9.2.2. Primary Endpoint Analysis

All the primary, secondary and explorative endpoints are defined in section 3.

If missing data is regarded as having a significant effect on the conclusions of the trial, sensitivity analyses with different methods for handling missing data will be included. Such methods may include complete case analyses, worst case/best case imputation and multiple imputation techniques.

9.2.2.1. Definition of endpoint(s)

All the primary, secondary and explorative endpoints are defined in section 3.

If missing data is regarded as having a significant effect on the conclusions of the trial, sensitivity analyses with different methods for handling missing data will be included.

Such methods may include complete case analyses, worst case/best case imputation and multiple imputation techniques.

9.3. Sample Size Determination

The study population consists of approximately 50 adult Norwegian patients newly diagnosed with PAI. The power analysis was performed for primary objective 1.1 applying 90% power and a two-sided significance level of 5%. For calculation of the required sample size, we make use of a formula for a parallel group design (30), n=2*(⟦σ/Δ)⟧^2*k , where σ is the standard deviation, Δ is the estimated clinically relevant difference, and k is a constant reflecting the chosen significance level and power. Based on a previous study, we estimate a standard deviation of 4 and a difference of 4 in AddiQoL scores between the two treatments (31,32). A two-sided level of significance at 0.05 and power at 0.90, gives k of 10.9. Put into the formula, we estimate a need for 2*(⟦4/4)⟧^2*10.9 = 21 study participants in each treatment group. Accounting for a 10% drop-out rate, we estimate a total need for at least 46 study participants.

risk of performing a type II errorof rejecting (Plenadren ≠ Cortison Of course, small

for the primary objective, “”score reported thus

For the secondary objectives conventional power calculations were not performed. However, our previous experience with clinical trials in PAI suggests that a participant number of approximately 50 should be enough to detect between-group differences in bone markers and cardiovascular variables (27).

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

The study will be performed in accordance with the protocol, the World Medical Association Revised Declaration of Helsinki (2008), the ICH Harmonized Tripartite Guideline for Good Clinical Practice, and any local regulations. The Ethics committee for medical research, Western Norway has granted permission to conduct the trial (ADNorGC). The patient will receive oral and written information concerning the study.

ROAS have ethical approval (REK 2013/1504) and is licensed by the Norwegian Data Protection Authority (1). This specific project was submitted to IEC in mid-2021, and an ethical approval has been obtained. Likewise, the project will be registered in the ClinicalTrials.gov database prior to study start.

All participants will receive thorough oral and written information before providing written consent for study participation. The participants are free to withdraw their consent at any time during the study. Clinical records and results will be archived in hospital records. Data will be collected to computerized research files without patient identifiers and stored according to the hospitals' research ethics guidelines. Biological research materials (blood samples) are coded and stored at laboratory at Haukeland University Hospital according to general regulations, D

Patients will be instructed to report any adverse events during the study period to the recruiting physician. If a patient develops conditions meeting the exclusion criteria or serious adverse events, the patient will be withdrawn from the study. The recruiting physician may also discontinue study participation at any time if it is considered necessary for any of the following reasons:

- Significant protocol deviation or violation.
- Significant failure to comply with study requirements.

Deviation log: We encourage doctors in charge of patients to report all deviations in the protocol to the coordinating investigator or medical monitor, as well as to register in the patient journal.

The study documentation and research data will be stored 5 years after the termination of the study. Professor Husebye will be responsible for this repository. After the termination of the study, the Regional Committee for medical and health research ethics will be notified. If needed to terminate the study earlier, we will notify the Regional Committee for medical and health research ethics within 15 days and the reason of the premature termination will be clarified.

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

- The protocol, protocol amendments, ICF, investigator's brochure and other relevant documents must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations

10.1.2. Financial Disclosure

The study is Financed by the Regional Health Authorities through the KlinBeForsk program

10.1.3. Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study.
- Potential participants will be informed that their participation is voluntary. They will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

- The medical record will include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants will be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

10.1.4. Recruitment strategy

All patients diagnosed with primary adrenal insufficiency in the age range 16-70 years of age in Norway during the active study period, will be asked to participate.

10.1.5. Data Protection

- Participants will be assigned a unique identifier by the sponsor when included in the national registry.
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.6. Dissemination of Clinical Study Data

The results will be published in peer-reviewed international journals. Results will also be disseminated to patients, policy makers and the general public.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.

- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site End of Study and Early Termination

End of study is defined as the last visit for the last patient (LPLV) in the study. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of Unsolicited and Solicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.
- Potential unsolicited AEs may be medically attended (i.e. symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participant will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participant and by review of available medical records at the next visit.
- Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease, or more severe than expected for the participant's condition)
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>not</u> Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.2.2. Definition of SAE

A SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the participant 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.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

10.2.3. Definition of suspected unexpected serious adverse reaction (SUSAR)

If an event is not an SAE per definition above, then it cannot be a SUSAR

SUSAR Definition

Adverse Reaction: all unwanted and unintended responses to an investigational medicinal product related to any dose administered.

Unexpected Adverse Reaction: an adverse reaction, the nature or severity of which is not consistent with the applicable product information (SmPC).

Suspected Unexpected Serious Adverse Reaction: Unexpected Adverse Reaction that:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect

Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

10.2.4. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor in lieu of completion of the AE/SAE form.
- There may be instances when copies of medical records for certain cases are requested by sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild:
  A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate:
  A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe:
  A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to sponsor within 24 hours of receipt of the information.

10.2.5. Reporting of SAEs

SAE Reporting to sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the sponsor by telephone.
- Contacts for SAE reporting can be found in Investigator's Site File (ISF).

SAE Reporting to sponsor via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in the ISF.

10.2.6. Reporting of SUSAR

The investigator will report SAE to the medical monitor. The medical monitor will evaluate if the SAE also is a SUSAR, if so, the medical monitor will report the SUSAR to the Competent Authority through Eudravigilance (EV).

Sponsor will ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible and in no case later than seven (7) days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight (8) days.

Other SUSARs will be reported no later than 15 days after the incident.

10.3. Appendix 10: Contact details

Sponsor:	**Helse-Bergen HF, Department of Medicine**
Coordinating Investigator	**Eystein Husebye, professor, consultant. PI (primary invetstigator) for Helse Vest, Helse Bergen** Department of Medicine, Haukeland University hospital, N-5021 Bergen Tel: 99404788 E-mail: eyhu@helse-bergen.no
Medical monitor:	**Sandra Dis Steintorsdottir, Ph.D. student, research fellow, consultant** Department of Medicine, Haukeland University hospital, N-5021 Bergen Tel: 47445641 E-mail: sandra.dis.steintorsdottir@helse-bergen.no
Participating Site:	**Helse Vest** **Marianne Øksnes, consultant, investigator** Department of Medicine, Haukeland University Hospital. Tel: 91384514 E-mail: Marianne.Oksnes@uib.no **Lars E. Breivik, register/database manager, investigator** Hormone laboratory, Haukeland University Hospital. Tel: 41663909

E-mail: lars.ertesvag.breivik@helse-bergen.no

Paal Methlie, consultant, investigator

Department of Medicine, Haukeland University Hospital.

Tel: 97677930

E-mail: paal.methlie@helse-bergen.no

Marianne Grytaas, consultant, investigator

Department of Medicine, Haukeland University Hospital.

Tel: 41545435

E-mail: marianne.aardal.grytaas@helse-bergen.no

Geir Hølleland, consultant, PI for Helse Førde.

Department of Medicine, Førde Hospital. Helse Førde.

Tel: 57831474

E-mail: geir.holleland@helse-forde.no

Ann-Elin Meling Stokland, consultant, investigator

Department of Medicine, Stavanger University Hospital.

Tel: 92032025

E-mail: ann-elin.meling.stokland@sus.no

Siri Carlsen, consultant, PI for Helse Stavanger

Department of Medicine, Stavanger University Hospital.

Tel: 95087620

E-mail: siri.carlsen@sus.no

Ida Kloster, consultant, PI for Helse Fonna.

Department of Medicine, Haugesund Hospital. Helse Fonna.

Tel: 48174825

E-mail: ida.kloster@helse-fonna.no

Sigfrid Christine Reisegg, consultant, PI for Haraldsplass HF.

Department of Medicine, Haraldsplass Hospital.

Tel: 97 06 93 87

E-mail: sigfrid.christine.reisegg@haraldsplass.no

Helse Nord

Guri Grimnes, assistant professor, consultant, PI for Helse Nord

Department of Medicine, University Hospital of Northern Norway, N-9038 Tromsø

Tel: 48058538

E-mail: Guri.grimnes@unn.no

Helse Midt

Halvard Singsås, consultant, investigator

Department of Medicine, St. Olav Hospital, N-9038 Trondheim

Tel: 90561595

E-mail: hallvard.singsas@stolav.no

Bjørn Olav Åsvold, consultant, PI for Helse Midt / St. Olavs hospital HF

Department of Medicine, St. Olav Hospital, N-9038 Trondheim

Tel: 92466240

E-mail: bjorn.o.asvold@ntnu.no

Dag-Eirik Sørmo, consultant, PI for Helse Nord-Trønderlag HF.

Department of Medicine, Levanger Hospital.

Tel: 97114736

E-mail: dag-eirik.sormo@helse-nordtrondelag.no

Marthe L. Rensvik, consultant, PI for Helse Møre og Romsdal.

Department of Medicine, Ålesund Hospital. Helse Møre og Romsdal.

Tel: 90 86 49 08

E-mail: Marthe.Landsverk.Rensvik@helse-mr.no

Thor Haug, consultant, investigator

Department of Medicine, Molde Hospital.

Tel: 71120000

E-mail: Thor.haug@helse-mr.no

Helse Sørøst

Anders Jørgensen, consultant, PI for Helse sør øst / OUS HF.

Department of Medicine, Oslo University hospital, N-0021 Oslo

Tel: 95582329

E-mail: andjo@ous-hf.no

Stina Therese Sollid, consultant, PI for Vestre Viken HF

Department of Medicine, Vestre viken, Drammen Hospital.

Tel: 93496216

E-mail: STTHSO@vestreviken.no

Margrethe Svendsen, consultant, PI for Østfold hospital HF.

Department of Medicine, Østfold Hospital, Moss.

Tel: 95967707

E-mail: margrethe.svendsen@so-hf.no

Ingrid Nermoen, consultant, PI for Akershus hospital (AHUS)

Department of Medicine, Akershus University Hospital.

Tel: 99639852

E-mail: Ingrid.Nermoen@ahus.no

Trine E. Finnes, consultant, PI for Innlandet hospital HF

Department of Medicine, Hamar Hospital

Tel: 99293135

E-mail: Trine.E.Finnes@sykehuset-innlandet.no

Aneta Ewa Tomkowicz, consultant, PI for Sørlandet hospital HF

Department of Medicine, Sørlandet Hospital, Kristiansand.

Tel: 38074318

E-mail: Aneta.Ewa.Tomkowicz@sshf.no

Aleksandra Debowska, consultant, PI for Vestfold hospital HF

Department of Medicine, Vestfold Hospital, Tønsberg.

Tel: 93047059

E-mail: Aleksandra.debowska@siv.no

Synnøve E. Holte, consultant, investigator

Department of Medicine, Sørlandet Hospital, Arendal

E-mail: Synnove.Emblem.Holte@sshf.no

Cooperating institutions

Institut of Neuromedicine and Movement Science, Fakulty of Medicine and Health Science, Norwegian University of Science and Technology (NTNU), Trondheim.
Tor Ivar Hansen, Ph.D., Psychologist.
Tel: 72822632
E-mail: torivar.hansen@ntnu.no

Institut of Biological and Medical Psychology, Bergen University.
Janne Grønli, professor, Ph.D., somnologist, research group leader.
Tel: 55586003
E-mail: janne.gronli@uib.no

11. References

1. (ROAS) Nkfoas. Årsrapport for 2019. Haukeland universitetssjukehus, Helse Bergen; 2019.

2. Johannsson G, Nilsson AG, Bergthorsdottir R, Burman P, Dahlqvist P, Ekman B, et al. Improved cortisol exposure-time profile and outcome in patients with adrenal insufficiency: a prospective randomized trial of a novel hydrocortisone dual-release formulation. J Clin Endocrinol Metab. 2012;97(2):473-81.

3. Espiard S, McQueen J, Sherlock M, Ragnarsson O, Bergthorsdottir R, Burman P, et al. Improved Urinary Cortisol Metabolome in Addison's disease: a Prospective Trial of Dual-Release Hydrocortisone. The Journal of clinical endocrinology and metabolism. 2020.

4. Nilsson AG, Bergthorsdottir R, Burman P, Dahlqvist P, Ekman B, Engstrom BE, et al. Long-term safety of once-daily, dual-release hydrocortisone in patients with adrenal insufficiency: a phase 3b, open-label, extension study. Eur J Endocrinol. 2017;176(6):715-25.

5. Husebye ES, Pearce SH, Krone NP, Kampe O. Adrenal insufficiency. Lancet. 2021;397(10274):613-29.

6. Erichsen MM, Lovas K, Skinningsrud B, Wolff AB, Undlien DE, Svartberg J, et al. Clinical, immunological, and genetic features of autoimmune primary adrenal insufficiency: observations from a Norwegian registry. J Clin Endocrinol Metab. 2009;94(12):4882-90.

7. Nowotny H, Ahmed SF, Bensing S, Beun JG, Brösamle M, Chifu I, et al. Therapy options for adrenal insufficiency and recommendations for the management of adrenal crisis. Endocrine. 2021;71(3):586-94.

8. Dunlop D. EIGHTY-SIX CASES OF ADDISON'S DISEASE. British medical journal. 1963;2(5362):887-91.

9. van der Valk ES, Smans LC, Hofstetter H, Stubbe JH, de Vries M, Backx FJ, et al. Decreased physical activity, reduced QoL and presence of debilitating fatigue in patients with Addison's disease. Clinical endocrinology. 2016;85(3):354-60.

10. Skov J, Sundstrom A, Ludvigsson JF, Kampe O, Bensing S. Sex-specific risk of cardiovascular disease in autoimmune Addison's disease - a population-based cohort study. The Journal of clinical endocrinology and metabolism. 2019.

11. Bjornsdottir S, Sundstrom A, Ludvigsson JF, Blomqvist P, Kampe O, Bensing S. Drug prescription patterns in patients with Addison's disease: a Swedish population-based cohort study. J Clin Endocrinol Metab. 2013;98(5):2009-18.

12. Rahvar AH, Haas CS, Danneberg S, Harbeck B. Increased Cardiovascular Risk in Patients with Adrenal Insufficiency: A Short Review. BioMed research international. 2017;2017:3691913.

13. Bensing S, Brandt L, Tabaroj F, Sjoberg O, Nilsson B, Ekbom A, et al. Increased death risk and altered cancer incidence pattern in patients with isolated or combined autoimmune primary adrenocortical insufficiency. Clin Endocrinol (Oxf). 2008;69(5):697-704.

14. Quinkler M, Ekman B, Zhang P, Isidori AM, Murray RD. Mortality data from the European Adrenal Insufficiency Registry-Patient characterization and associations. Clinical endocrinology. 2018;89(1):30-5.

15. Bjornsdottir S, Saaf M, Bensing S, Kampe O, Michaelsson K, Ludvigsson JF. Risk of hip fracture in Addison's disease: a population-based cohort study. J Intern Med. 2011;270(2):187-95.

16. Løvås K, Gjesdal CG, Christensen M, Wolff AB, Almås B, Svartberg J, et al. Glucocorticoid replacement therapy and pharmacogenetics in Addison's disease: effects on bone. European journal of endocrinology / European Federation of Endocrine Societies. 2009;160(6):993-1002.

17. Choudhury S, Lightman S, Meeran K. Improving glucocorticoid replacement profiles in adrenal insufficiency. Clinical endocrinology. 2019.

18. Øksnes M, Ross R, Løvås K. Optimal glucocorticoid replacement in adrenal insufficiency. Best practice & research Clinical endocrinology & metabolism. 2015;29(1):3-15.

19. Karanatsios B, Prang KH, Verbunt E, Yeung JM, Kelaher M, Gibbs P. Defining key design elements of registry-based randomised controlled trials: a scoping review. Trials. 2020;21(1):552.

20. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. Ann Med. 2001;33(5):350-7.

21. Oksnes M, Bensing S, Hulting AL, Kampe O, Hackemann A, Meyer G, et al. Quality of life in European patients with Addison's disease: validity of the disease-specific questionnaire AddiQoL. J Clin Endocrinol Metab. 2012;97(2):568-76.

22. Isidori AM, Venneri MA, Lenzi A et al. Effect of once-daily, modified-release hydrocortisone versus standard glucocorticoid therapy on metabolism and innate immunity in patients with adrenal insufficiency (DREAM): a single-blind, randomised controlled trial. *The lancet Diabetes & endocrinology*. 2018;6(3):173-185.

23. Venneri MA, Hasenmajer V, Isidori AM et al. Circadian Rhythm of Glucocorticoid Administration Entrains Clock Genes in Immune Cells: A DREAM Trial Ancillary Study. *J Clin Endocrinol Metab*. 2018;103(8):2998-3009.

24. Giordano R, Guaraldi F, Marinazzo E, Fumarola F, Rampino A, Berardelli R, et al. Improvement of anthropometric and metabolic parameters, and quality of life following treatment with dual-release hydrocortisone in patients with Addison's disease. Endocrine. 2016;51(2):360-8.

25. Blackwell T, Ancoli-Israel S, Redline S, Stone KL. Factors that may influence the classification of sleep-wake by wrist actigraphy: the MrOS Sleep Study. J Clin Sleep Med. 2011;7(4):357-67.

26. Toften S, Pallesen S, Hrozanova M, Moen F, Grønli J. Validation of sleep stage classification using non-contact radar technology and machine learning (Somnofy®). Sleep Med. 2020;75:54-61.

27. Saevik AB, Akerman AK, Husebye ES, Oksnes M et al. Residual Corticosteroid Production in Autoimmune Addison Disease. *J Clin Endocrinol Metab*. 2020;105(7)..

28. Hafrstrom ECD HT, Haberg AK. Comparing web-based neuropsychological testing with standardized pen and paper versions, NTNU; 2013.

29. Hansen TI EH, Lehn H, Pintzka CWS, Håberg A. Successful implementation of internet based cognitive testing2012.

30. TI H, H L, HR E, AK H. Initial assessment of reliability of a self-administered web-based neuropsychological test battery. Computers in Human Behavior. 2016;63:91-97.