GLEPAGLUTIDE

CLINICAL TRIAL PROTOCOL ZP1848-17111

EASE SBS 1

A PHASE 3, INTERNATIONAL, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF GLEPAGLUTIDE IN PATIENTS WITH SHORT BOWEL SYNDROME (SBS)

Sponsor	Zealand Pharma A/S Sydmarken 11 DK-2860 Søborg Denmark
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Protocol version 3	21-Aug-2018
Protocol version 2	31-Jul-2018
Protocol version 1	31-May-2018

The trial will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki and with other applicable regulatory requirements.

PROTOCOL APPROVAL / SIGNATURE PAGE

Protocol ZP1848-17111 Version 10.0 Dated: 27-Jan-2022

EASE SBS 1

A Phase 3, international, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of glepaglutide in patients with short bowel syndrome (SBS)

[redacted] MD, Ph.D.

[redacted] 1/27/2022

Signature Medical Responsible Date

[redacted] Ph.D.
Principal Clinical Trial Manager

[redacted] 1/27/2022

Signature Principal Clinical Trial Manager Date

[redacted] Statistical Project Director

[redacted] 1/27/2022

Signature Statistical Project Director Date

[redacted] MD, Ph.D.
International Coordinating Investigator

[redacted] 1/27/2022

inating Investigator Date

1 Synopsis

Title of Trial: A Phase 3, international, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of glepaglutide in patients with short bowel syndrome (SBS) **Short Title**: EASE SBS 1 (Efficacy And Safety Evaluation of Glepaglutide in treatment of SBS)	
Trial center(s): Approximately 33 sites in Europe and North America	
Studied period (years): Estimated date first patient enrolled: Q3 2018 Estimated date last patient completed: Q3 2022	**Phase of development:** 3
Objectives: **Primary Objective:** To confirm the efficacy of glepaglutide in reducing parenteral support (PS) volume in SBS patients **Secondary Objectives:** • To evaluate the efficacy of glepaglutide on other efficacy endpoints in patients with SBS • To evaluate the safety and tolerability of glepaglutide in patients with SBS	
Methodology: This is a multicenter, placebo-controlled, randomized, parallel-group, double-blind, fixed dose, Phase 3 trial to demonstrate the superiority of once weekly and twice weekly subcutaneous (SC) injections of 10 mg glepaglutide versus placebo in stable SBS patients. After providing informed consent and initial confirmation of eligibility during the 2-week Screening period, patients will enter a PS Optimization and Stabilization Phase before baseline measurements are performed. An individual drinking menu will be defined by the patient and the Investigator during the Screening period and until the end of the Optimization Phase. All patients will be equipped with an electronic diary (eDiary) for recording of trial relevant data/information. Unless otherwise specified, baseline is defined as Day 1, prior to first dosing of trial product. Optimization Phase During the Optimization Phase, the Investigator may change the PS volume and content if the patient is considered unstable or not optimized. Any changes in PS volume or content will be administered according to institutional standard practice. The effect of any PS optimizations must be investigated after 2 weeks. Prior to an Optimization Phase visit, the patient must measure his/her urine over 48 hours, while adhering to the pre-defined drinking menu, and report the urine volume and oral fluid intake in the eDiary. PS optimization consist of 2 rounds, which limits the Optimization Phase to a maximum duration of 4 weeks (± 4 days).). If optimization cannot be shown during the 4-week period, a second Optimization Phase of up to 4 weeks (± 4 days) is allowed. The last Optimization Phase visit can be combined with the first visit in the Stabilization period if the patient is considered optimized. Stabilization Phase The Stabilization Phase has a minimum duration of 2 weeks and a maximum duration of 4 weeks (± 4 days). The last visit of the Optimization Phase can also be the first visit of the Stabilization Phase. Prior to the Stabilization Phase visit, the patient must measure his/her urine over 48 hours, while adhering to the pre-defined drinking menu, and report the urine volume and oral fluid intake in the eDiary. Patients will be evaluated every 2 weeks during the Stabilization Phase and will need to fulfill the pre-specified stability criteria before the patient can be randomized. If stability cannot be shown during the 4-week period due to unforeseen events such as infections, illness or similar, a second Stabilization Phase of up to 4 weeks (± 4 days) is allowed.	

A patient will be considered stable if all the following criteria are met:

- Actual PS usage (volume and content) matches prescribed PS (± 10% deviation in volume is acceptable) and
- 48-hour urine volumes at 2 consecutive visits within a 2-week interval (± 4 days, i.e., visits should be 10 to 18 days apart) are similar (a maximum of ± 25% deviation is acceptable), while the oral fluid intake is constant (the two 48-hour oral intakes differ less than 10%) and maximum 3.5 L per day and
- Urine volume is on average ≥ 1 L and ≤ 2.5 L per day.

The Investigator and Medical Monitor must both agree and approve that the patient has met the criteria to be considered stable after completing the Stabilization Phase.

The baseline PS volume (L/week) will be defined as the actual PS volume received during the 7-day period prior to Visit 1 (Day 1). The baseline daily urine volume (L per day) will be defined as the average of the last two 48-hour urine volume measures from the Stabilization Phase. For scheduling of the 48-hour measurement periods throughout the trial, see Table 4.

Main trial period:

Visit 1 is done within 2 weeks after the last Stabilization Phase visit. All eligible patients who complete the Optimization and Stabilization Phases will be randomized in a 1:1:1 manner to receive either: a) glepaglutide 10 mg twice weekly, b) glepaglutide 10 mg once weekly and placebo once weekly, or c) placebo SC twice weekly for the following 24 weeks.

During the 24-week Treatment Phase, PS need will be evaluated by 48-hour balance periods involving urine measurements and during which patients will be required to keep to an individually pre-defined drinking menu (timing, volume, and content) and document this in the eDiary.

The actual volume of PS will be recorded on an ongoing basis in electronic diaries (eDiaries) by the patients. The Investigator will record the type, content, and volume of the PS being used. Once trial drug treatment is initiated, PS volume can be adjusted at trial visits (at Weeks 1, 2, 4, 8, 12, 16, 20, and 24) if the criteria for adjustment are met and according to a predefined algorithm.

Algorithm for PS volume reduction:

IF: daily average urine volume of the current visit is at least 10% higher than baseline urine volume.

THEN: New PS volume (weekly) = Current PS volume (weekly) – 7 x absolute increase in daily urine volume from baseline

The Investigator may arrange unscheduled visits (preceded by a 48-hour balance period) if he or she considers the visits to be needed based on medical judgement to assess PS volume needs.

It is acknowledged that intake of oral liquids and PS might have to be changed between scheduled visits to avoid edema, especially if treatment is effective. In such cases changes to the PS is at the discretion of the Investigator and the reason needs to be documented in the eCRF.

Any changes to the content of PS are left to the discretion of the Investigator and the reason is documented in the eCRF.

After completing the Treatment Phase, all patients (patients in all 3 treatment groups) will be eligible to enter an Extension Trial and receive glepaglutide. In addition, patients who were dosed but discontinued from trial treatment due to reasons other than an unacceptable adverse event (AE) related to the trial product or withdrawal of consent may be invited to enter the Extension Trial when completing the 24-week Treatment Phase schedule. For patients not entering the Extension Trial, a Follow-up Visit will be conducted 4 weeks after completion of the Treatment Phase.

Target Patient Population:

Key patient inclusion criteria include:

- Diagnosis of SBS defined as remaining small bowel in continuity of estimated less than 200 cm [equal to 79 inches] with the latest intestinal resection being at least 6 months prior to Screening and where the patient is considered stable with regard to PS needs. No restorative surgery planned in the trial period.
- PS requirement of at least 3 days per week as assessed prior to Screening and at the end of the Optimization and Stabilization Phases.
- Willing to adhere to an individual pre-defined drinking menu and urine measurement during the 48-hour measuring intervals.
- Age ≥ 18 years and ≤ 90 years at Screening.
- At randomization: Maintains a stable PS volume for at least 2 weeks prior to randomization.

Trial products, dosage and mode of administration:

Glepaglutide: Provided in single-use vials containing 1 mL (an extractable volume of 0.5 mL) of a clear, essentially colorless solution for injection, containing 20 mg/mL glepaglutide. Patients randomized to active treatment will inject 10 mg (0.5 mL) glepaglutide either a) twice weekly or b) once weekly and placebo once weekly.

Reference therapy: Placebo is provided in single-use vials containing 1 mL (an extractable volume of 0.5 mL) of clear, essentially colorless solution for injection. Patients randomized to placebo treatment will inject (0.5 mL) placebo solution twice weekly.

Intervention groups and duration:

Duration of treatment is 24 weeks across treatment groups.

- Glepaglutide twice weekly: 10 mg glepaglutide on Day 1 and on Day 4 or 5 (same days of the week every week)
- Glepaglutide once weekly: 10 mg glepaglutide or placebo on Days 1 and on Day 4 or 5 (same days of the week every week)
- Placebo: placebo on Day 1 and on Day 4 or 5 (same days of the week every week)

Endpoints:

Primary Endpoint:

Reduction in weekly PS volume from baseline to Week 24

Key secondary endpoints:

- Clinical response, defined as achieving at least 20% reduction in weekly PS volume from baseline to both Weeks 20 and 24
- Reduction in days on PS ≥ 1 day/week from baseline to Week 24
- Reduction in weekly PS volume from baseline to Week 12
- Reduction in weekly PS volume of 100% (weaned off) at Week 24

Secondary efficacy endpoints:

- Reduction of at least 20% in PS volume from baseline to both Weeks 12 and 24
- Change in fluid composite effect (FCE) from baseline to Week 24
- Reduction in calculated energy content of parenteral macronutrients from baseline to Week 24
- Reduction in number of days on PS per week from baseline to Week 24
- Reduction of at least 40% in PS volume from baseline to both Weeks 20 and 24
- PGIC improvement at Weeks 4, 12, 20, and 24

- Change in weight from baseline to Week 24

Other efficacy endpoints:

- Reduction in days on PS ≥ 2 days/week from baseline to Week 24
- Reduction in days on PS ≥ 3 days/week from baseline to Week 24
- Reduction in duration of PS infusions per week from baseline
- Concentration trough levels of glepaglutide and metabolites
- Change in plasma citrulline level from baseline to Week 24
- Change in weekly need for parenteral micronutrients (sodium, potassium, magnesium and calcium) from baseline to Week 24
- Change in patient-reported outcomes (SBS-I and EQ-5D-5L) from baseline to Week 24
  - Reduction in bowel movements or stoma bag emptying from baseline to Week 24 Safety endpoints:
- Incidence and types of AEs and serious adverse events (SAEs)
- Change in clinical evaluations:
- Vital signs
- Electrocardiogram (ECG)
- Change in safety laboratory assessments:
- Hematology
- Biochemistry
- Urinalysis
- Standard bone markers
- Immunogenicity

Statistical methodology:

Inferential statistical analyses of the primary and secondary efficacy endpoints will be performed. All comparisons will be between each glepaglutide treatment group and placebo. No statistical interim analysis is planned.

Analysis Sets

- The Full Analysis Set (FAS) will consist of all randomized patients, who received at least one dose of trial drug (glepaglutide or placebo). All efficacy analyses will be based on the FAS.
- The Per-protocol Analysis Set will consist of all FAS patients who do not experience any major protocol deviations. Final judgments on exclusion from the Per-protocol Analysis Set will be made prior to database lock. The Per-protocol Analysis Set will be used for supplementary analyses of the primary and key secondary efficacy endpoints.
- The Safety Analysis Set will consist of all randomized patients, who received at least 1 dose of trial drug (glepaglutide or placebo). This is the same definition as for the FAS, but the two can deviate in special circumstances. All safety analyses will be based on the Safety Analysis Set.

Analysis of primary and key secondary endpoints

The primary analysis of the primary efficacy endpoint uses a restricted maximum likelihood–based repeated-measures approach to compare treatment groups with respect to the mean change from baseline in weekly PS volume at Week 24. The model will use weekly PS volume assessments at Week 1, 2, 4, 8, 12, 16, 20, and 24, and will include the covariates for treatment group, baseline weekly PS volume, visit (categorical variable), stratification factor (weekly PS volume requirements <12 L/week versus >12 L/week), and visit-by-treatment group interaction. Missing values will be

imputed using multiple imputation methods. For the primary analysis, a Copy Reference approach is used with placebo treatment as reference, while for sensitivity analyses, a Jump to Reference and a Copy Incremental from Reference approaches will be applied. As a supplementary analysis, the analysis will be repeated using the Per-protocol Analysis Set.

The 4 key secondary efficacy endpoints will be analyzed to assess the treatment effect using the FAS. Continuous endpoints will be analyzed in a similar manner as the primary efficacy endpoint. The binary endpoint of clinical response will be tested using the Cochran-Mantel-Haenszel test with stratification on the randomization stratification factor (weekly PS volume requirements <12 L/week versus >12 L/week). As a supplementary analysis, the 4 key secondary endpoints analyses will be repeated using the Per-protocol Analysis Set.

Gatekeeping Procedure

A parallel gatekeeping testing procedure will be used to protect the overall type I error rate of α testing the primary endpoint together with the key secondary endpoints between each glepaglutide treatment group versus placebo. The twice weekly treatment group and once weekly treatment group comparisons to placebo will be tested by splitting α into 2 α/2 comparisons.

Secondary endpoints

The secondary efficacy endpoints will be analyzed to assess the treatment effect using the FAS. The tests will be non-hierarchical and type I error will not be adjusted for multiple testing. The other efficacy endpoints will be summarized to assess the treatment effect using the FAS. Only descriptive statistics will be presented for these other efficacy endpoints and no inferential statistics will be performed.

Safety Analysis

All safety analyses will be conducted using the Safety Analysis Set. No inferential tests of safety data will be performed. Descriptive summaries of safety data will be presented. Adverse events (treatment-emergent unless otherwise specified) will be presented by system organ class (SOC) and preferred term (PT) for each treatment group.

Discontinuations and Data Handling Rules

The analysis for the primary efficacy endpoint as well as for the continuous key secondary efficacy endpoints will handle missing values using a CR-imputed data set generated from the multiple imputation approach described for the primary efficacy endpoint. For all responder analyses, patients who discontinue for any reason will be considered as non-responders from the time of discontinuation onwards. No pooling of sites is planned for the efficacy analyses.

Number of patients (planned):

Approximately 108 patients are planned to be randomized into the trial 1:1:1.

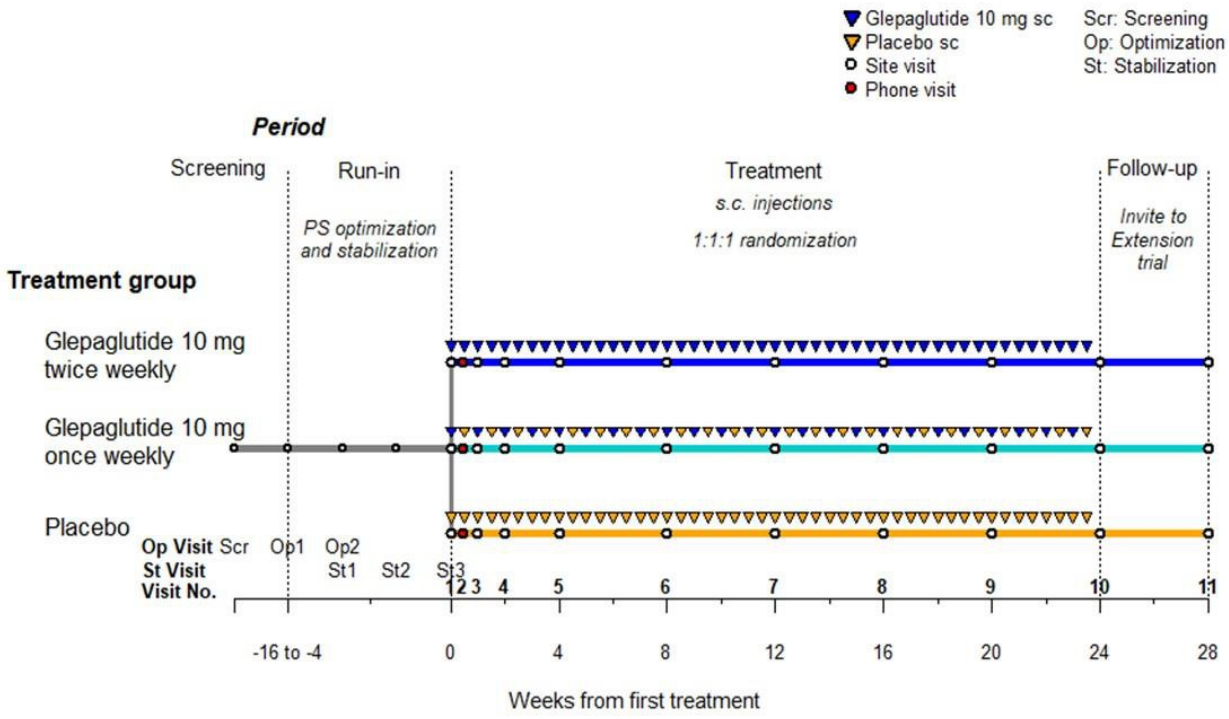

Figure 1: Trial Design

ZEALAND PHARMA

Table 1: Schedule of Assessments

Phase	Screening	Run in: PS optimization phase	Run-in: PS stabilization phase	Treatment phase									EOT	FU[19]
Visit day or week Time window (days)	up to 14 d prior to Op1	Duration: 2 to 4 weeks ±4d*	Duration: 2 to 4 weeks ±4d*	D1[18]	D3 ±1	D8 ±2 (W1)	D15 ±3 (W2)	D29 ±5 (W4)	D57 ±5 (W8)	D85 ±5 (W12)	D113 ±7 (W16)	D141 ±7 (W20)	D169 ±7 (W24)	D197 ±7 (W28)
Visit #	Sc	Op1, Op2 etc.	St1, St2 etc.	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	FU
Visit type (site, phone)	S	S	S	S	P	S	S	S	S	S	S	S	S	S
Informed consent	X[1]													
Inclusion/exclusion criteria	X			X										
Demographics (age, gender, race and ethnicity [if allowed in the participating country])	X													
Medical history and concomitant illness	X[2]													
SBS characteristics	X													
PS regimen (day, volume, and content)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Definition of individual drinking menu (volume, content & timing)[4]	X	X												
Body weight/height (height at Sc only)[5]	X	X	X	X		X	X	X	X	X	X	X	X	X
Concomitant medications/procedures	X	X	X	X		X	X	X	X	X	X	X	X	X
ECG	X			X						X			X	
Vital signs (heart rate, blood pressure, body temp)	X	X	X	X		X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination (Full PE at Sc; SBS symptom-driven at all other visits)	X (full)			X		X	X	X	X	X	X	X	X	X
Colonoscopy	X[6]													
Laboratory														
Urine sample[7]	X	X	X	X		X	X	X	X	X	X	X	X	X
Pregnancy test for females of childbearing potential only	X	X	X	X				X	X	X	X	X	X	X
Hematology and Biochemistry [8, 9, 10]	X	X	X	X		X	X	X	X	X	X	X	X	X
Citrulline[11]				X				X					X	X
PK[11]				X		X	X	X	X	X	X	X	X	X

Phase	Screening	Run in: PS optimization phase	Run-in: PS stabilization phase	Treatment phase									EOT	FU[19]
Visit day or week Time window (days)	up to 14 d prior to Op1	Duration: 2 to 4 weeks ±4d*	Duration: 2 to 4 weeks ±4d*	D1[18]	D3 ±1	D8 ±2 (W1)	D15 ±3 (W2)	D29 ±5 (W4)	D57 ±5 (W8)	D85 ±5 (W12)	D113 ±7 (W16)	D141 ±7 (W20)	D169 ±7 (W24)	D197 ±7 (W28)
Visit #	Sc	Op1, Op2 etc.	St1, St2 etc.	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	FU
Visit type (site, phone)	S	S	S	S	P	S	S	S	S	S	S	S	S	S
Anti-drug Antibodies[11]				X			X	X	X	X			X	X
Bone Markers[12]				X									X	
HIV, hepatitis B, hepatitis C	X													
Diary: 48-hour oral fluid intake, fixed drinking menu		X	X	X**		X	X	X	X	X	X	X	X	X
Diary: 48-hour urine volume		X	X	X**		X	X	X	X	X	X	X	X	X
Diary 48-hour: Colon-in-continuity patients: Number of bowel movements Stoma patients: Number of stoma bag emptying			X	X**		X	X	X	X	X	X	X	X	X
Diary: PS use		X	X	X	X	X	X	X	X	X	X	X	X	X
Diary: Trial product administration (date and time of the day) + injection site (abdomen, thigh)				X										
SBS-I[13]		X	X	X		X	X	X	X	X	X	X	X	X
EQ-5D-5L[13]		X	X	X						X			X	X
PGIC[13]								X		X		X	X	
Exit interviews (Danish, French, German, UK and US sites only)													X	
Randomization				X										
Decision on dosing days schedule				X	(X)[14]									
Dispense trial product				X[15]				X	X	X	X	X		
Trial product return and accountability[16]						X	X	X	X	X	X	X	X	
Compliance check[17]				X	X	X	X	X	X	X	X	X	X	
Final Visit[19]													X	X

Abbreviations: d=day; FU=Follow-up; Op=Optimization Phase visit; SBS=short bowel syndrome; Sc=Screening visit; St=Stabilization Phase visit; V=visit; W=week

* If optimization/stabilization cannot be shown during the 4-week period, a second Optimization/Stabilization Phase of up to 4 weeks (± 4 days) is allowed.

** In case the patient is considered stable at the last two St Visits, it is not needed to conduct another 48-hour period prior to Visit 1.

1. Informed consent must be obtained before any trial related assessments incl. the start of the 48-hour oral fluid intake and urine volume measurement. Informed consent may be obtained prior to the Screening Visit.
2. Including detailed information on whether the patient has a history of encephalopathy, ascites, cholestasis, steatosis, and/or cirrhosis. If yes, the outcome / histopathologic diagnosis and date of histopathologic diagnosis is reported. Any history of drug/alcohol abuse is reported. Information on smoking and current use of alcohol will be reported.
3. PS regimen will be based on information from the eDiary.
4. Define 24-hour drinking menu, which will be repeated twice during the 48 hour balance periods. It can be adjusted until the end of the Optimization Phase. After this, it may not be changed. Provide information and instructions to patients for documentation in eDiary.
5. Patients are encouraged to measure their body weight at home weekly to detect fluid retention early. If the weight changes, patients should call the trial site for guidance.
6. For patients with remnant colon, colonoscopy should be performed and evaluated before start of Optimization Phase. Colonoscopies performed as part of routine clinical practice (and prior to provision of informed consent) up to 6 months prior to Screening (Sc) are acceptable. In case a remnant colon is not connected to the passage of foods and thereby dormant, a computerized tomography (CT) scan or magnetic resonance imaging (MRI) (if standard of care at site) will suffice at the discretion of the Investigator to document the absence of concerns regarding malignancy.
7. Urinalysis: Blood, glucose, leukocytes, pH, osmolality, protein, sodium, and potassium.
8. Hematology: Hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelet count. Biochemistry: Sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, estimated CLcr, glucose, calcium, phosphorous, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), international normalized ratio (INR), gamma-glutamyl transferase (GGT), lactic dehydrogenase, conjugated bilirubin, total bilirubin, total protein, albumin, amylase, uric acid, C-reactive protein (CRP). In case of suspected liver injury based on increased ALT, AST, alkaline phosphatase, or total bilirubin, the tests should be repeated at 48-72 hours for evaluation of the event course/confirmation.
9. In addition, cholesterol and triglycerides will be measured orally fasting at visits 1 (Day 1) and Visit 10 (Day 169/Week 24).
10. In addition, magnesium and zinc will be measured at visits 1 (Day 1), 7 (Day 85/Week 12) and 10 (Day 169/Week 24).
11. Blood draws for PK, ADA, and citrulline sampling must be done prior to dosing, if dosing occurs on the day of the visit. In case of treatment discontinuation, the patient will be asked to come for ADA sampling at EOT (End of Treatment) as well as approximately four weeks after treatment discontinuation.
12. Bone markers include: 25OH vitamin D, parathyroid hormone (PTH), thyroid stimulating hormone (TSH; thyrotropin), P-CTx (collagen I, C-terminal telopeptide-fragments), and P-PINP (Pro-collagen, N-terminal pro-peptide).
13. Questionnaires must be completed at site visits prior to any other trial related assessment. It is recommended that the PGIC is completed first, followed by the SBS-I, then the EQ-5D-5L. The SBS-I and EQ-5D-5L are to be completed once during PS optimization phase, at the start of and after the stabilization phase, and all PROs are to be completed during treatment as indicated in the Schedule of Assessments. The exit interviews (Danish, French, German, UK and US sites only sites only) will be conducted no longer than 7 days after EOT visit.
14. Remind patient of the next dosing day.
15. Train the patient to self-inject.
16. Patient should be instructed to return all used vials on an ongoing basis.
17. Treatment compliance should be discussed with the patient to ensure that the medication is being taken correctly and that a new vial is used for each injection.
18. Visit 1 should be done within 2 weeks after the last Stabilization Phase. If done on the same day, Visit 1 lab samples should be drawn.
19. Patients entering the Extension Trial will have Final visit at Visit 10. Patients not entering the Extension Trial should come to the follow-up, including handing in the eDiary.