CLINICAL STUDY PROTOCOL

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(France)

A SINGLE AND MULTIPLE ASCENDING DOSE STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF AZP-3601, A SYNTHETIC PARATHYROID HORMONE ANALOG, IN HEALTHY SUBJECTS AND IN SUBJECTS WITH HYPOPARATHYROIDISM

Sponsor code: AZP-3601-CLI-001
PRA code: AZP20005-20005X
EudraCT number: 2020-003295-41

AZP-3601 SAD and MAD study

Investigational product:	AZP-3601
Clinical phase:	Phase 1
Indication to be studied:	Hypoparathyroidism
Sponsor:	Amolyt Pharma 15, chemin du Saquin Espace Européen, Building G 69130 Écully France
Contract Research Organization:	PRA Health Sciences (PRA) – Early Development Services (EDS) Van Swietenlaan 6 9728 NZ Groningen The Netherlands
[redacted]	[redacted]
[redacted]	[redacted]
Clinical Sites (Subjects with hypoparathyroidism - Part C):	Approximately 10 to 12 clinical sites in Europe

This study will be performed in compliance with the principles of Good Clinical Practice.

SYNOPSIS

Study Title
A SINGLE AND MULTIPLE ASCENDING DOSE STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF AZP-3601, A SYNTHETIC PARATHYROID HORMONE ANALOG, IN HEALTHY SUBJECTS AND IN SUBJECTS WITH HYPOPARATHYROIDISM

Short Study Title
AZP-3601 SAD and MAD study

Study Codes
Sponsor code : AZP-3601-CLI-001
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EudraCT number : 2020-003295-41

Clinical Phase
Phase 1

Indication to be Studied
Hypoparathyroidism (HP)

Sponsor
Amolyt Pharma

Contract Research Organization
PRA-EDS

[redacted]

Clinical Sites for Part C in Patients with HP
Approximately 10 to 12 clinical sites in Europe

Objectives
Primary

- [redacted]
- To assess the safety and tolerability of AZP-3601 following single and 4-week multiple ascending doses administered by sc injection to patients with HP (Part C, Main Treatment Period)
- To assess the safety and tolerability of AZP-3601 during a 2-month treatment extension period (Part C, Extension Phase) in patients with HP

Secondary

- [redacted]
- To assess the PD response of AZP-3601 on maintenance of serum calcium and phosphate levels within a target range while oral calcium and active vitamin D are progressively reduced, following multiple ascending doses administered by sc injection to patients with HP (Part C, Main Treatment Period)

- To assess the PK of AZP-3601 following single and multiple ascending doses administered by sc injection to patients with HP (Part C)
- To assess the feasibility of individual titration of AZP3601 during a 2-month treatment extension period (Part C, Extension Phase) in patients with HP (ie if individual dosing across a dose range can be implemented in a safe and effective manner and can be maintained throughout the treatment period)

Exploratory

- [redacted]
- To assess the effect of AZP-3601 on urinary excretion of calcium and phosphate as well as on bone turnover biomarkers following multiple ascending doses administered by sc injection to patients with HP (Part C, Main Treatment period)
- To assess the effect of AZP-3601 on urinary excretion of calcium and phosphate as well as on bone biomarker and Bone Mineral Density (BMD) as assessed by Dual-Energy X-Ray absorptiometry (DXA) during a 2-month treatment extension period (Part C, Extension Phase)

Design and Treatments

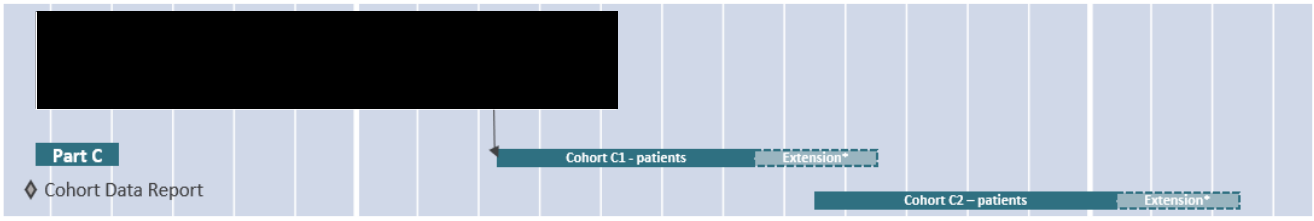
This is a first-in-human (FIH) study in healthy subjects followed by a study in patients with HP combined in a single protocol. [redacted]

Part B will be followed by a MAD part in patients with HP who will receive AZP3601 for 4 weeks (Part C, Main Treatment period).

Patient completing the 4 weeks Main Treatment Period of Part C, will be offered to enter a 2-month open label treatment extension phase. Together with the initial 4-weeks treatment period, this extension phase will allow the collection of safety and PD data over a total of 3 months of treatment.

In all study parts, safety, tolerability, PK (Part [redacted] C), and PD of sc doses of AZP-3601 will be assessed.

The overall study schematic is presented in the figure below:



[redacted]

[redacted]

[redacted]

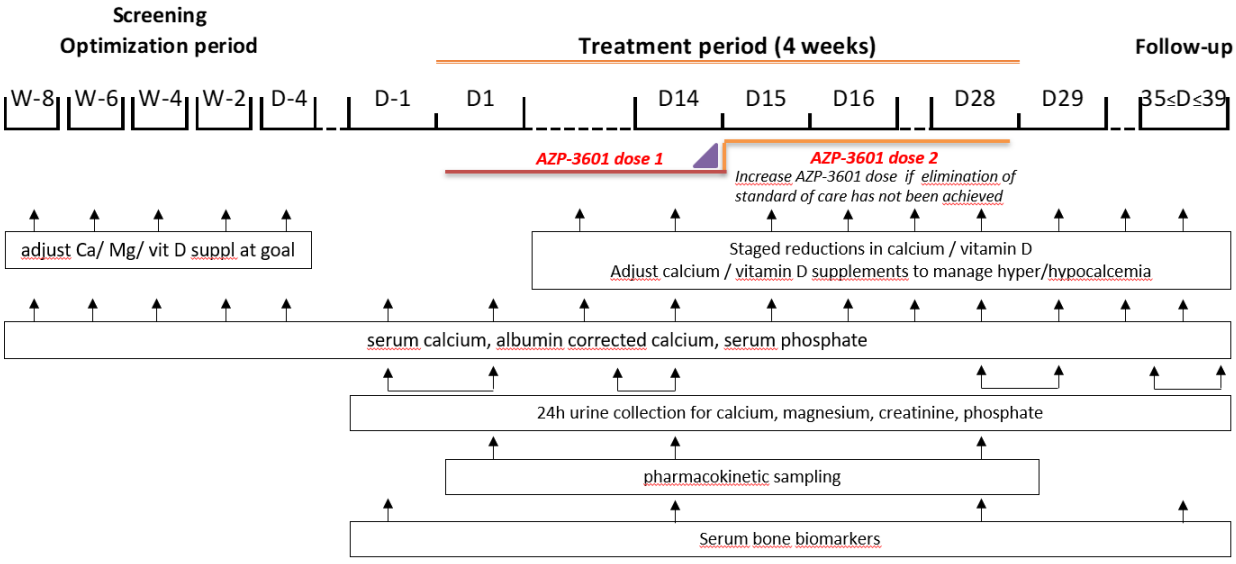
[redacted]

Part C (MAD part in patients with HP)

Part C will be an open-label MAD study in male or female subjects with HP who are on treatment with oral calcium and active vitamin D to evaluate the safety and tolerability, PK , and PD of AZP-3601. Up to 2 cohorts of approximately 12 patients each are planned for this part of the study.

Part C, Main Treatment Period

The overall study schematic for the Main Treatment Period of Part C, is presented hereafter (for more details, please refer to the Schedule of Assessments – Part C in Table 3):



Prior to the treatment period, there will be an optimization period of up to 8 weeks during which doses of oral calcium and active vitamin D will be adjusted to achieve a baseline target range of albumin-corrected serum calcium (7.8 to 9.0 mg/dL, ie, 1.95 to 2.25 mmol/L) and therefore ensuring a close baseline for all patients.

During this optimization period, any serum 25-hydroxy vitamin D (native vitamin D) and/or magnesium deficiencies will be corrected.

During the treatment period, patients in Part C will receive AZP-3601 for 28 days as daily sc abdominal injections (with rotation of injection sites every dosing day).

Doses of oral calcium and active vitamin D supplements will be carefully reduced during the initial 14 days of treatment while maintaining albumin-corrected serum calcium in the target range (7.8 to 9.0 mg/dL, ie, 1.95 to 2.25 mmol/L). Reductions of both oral calcium and active vitamin D supplements will be performed using a staged approach until the active vitamin D dose can be eliminated and the oral calcium dose can be reduced to or below 500 mg/day (please note that throughout this protocol doses of oral calcium refer to doses of elemental calcium). Based on animal data, serum calcium is expected to increase progressively following repeated administration of AZP-3601 and PD steady state is expected to be observed within the first 5 days of dosing. Staggered reductions of doses of oral calcium and active vitamin D supplements will therefore be performed at near-steady state based on the predose albumin-corrected serum calcium value. It is anticipated to perform reduction of supplements on Day 5, 8, and 11 (Cohort C1). The days of dose reduction of supplements for Cohort C2 have been changed to Days 3, 5 and 8 based on data from Part B and from Part C Cohort C1.
If independence from active vitamin D and reduction of oral calcium is not achieved on Day 14 (ie, elimination of active vitamine D and reduction of oral calcium to or below 500 mg/day), the AZP-3601 dose will be increased and patients will be treated at this dose for the remaining duration of the treatment period (up to Day 28). In addition, staggered reductions of doses of oral calcium and active vitamin D supplements will therefore be performed and/or continued during the second 14 days of the Main Treatment Period according to the same principles as the first 14 days of the Main Treatment Period.

Patients achieving independence from active vitamin D and reduction of oral calcium on Day 14 will remain at the same dose level. The last remaining daily dose of oral calcium, if any, may be removed on Day 17 based on the predose albumin-corrected value of serum calcium.

Patients will undergo frequent testing for albumin-corrected serum calcium and phosphate during the initial 14-day treatment period and again following increase of the dose. In addition, there may be additional and unscheduled checks for albumin-corrected serum calcium and phosphate at the discretion of the Investigator.

At any time during the study, hypercalcemia and hypocalcemia will be managed by adjustment in active vitamin D and/or oral calcium supplementation. Adjustments will be based on laboratory values including albumin-corrected serum calcium and serum phosphate as well as on symptoms and will be performed at the Investigator's judgment. As a general guidance, adjustments should be performed when calcium values are outside the target range of 7.8 to 9.0 mg/dL, ie, 1.95 to 2.25 mmol/L.

The following treatments are administered in Part C in an open-label fashion:

Cohort C1: multiple sc doses of 20 µg AZP-3601 (n=12) qd from Day 1 to Day 28 (dose increase of AZP-3601 to 40 µg was allowed from Day 14 onwards)

Cohort C2[b]: multiple sc doses of a fixed dose of 10[a] µg AZP-3601 (n=12) qd from Day 1 to Day 28 (dose of AZP-3601 may be increased at a fixed dose of 20[a] µg from Day 14 onwards)

During the extension phase, patients may have their AZP-3601 dose increased in increments of 10[a] µg to a maximum dose of 60[a] µg (Cohort 1) and of 80[a] µg (Cohort 2)

[a] The planned dose levels (including the dose levels allowed to increase the dose in the same cohort) may be changed following review of data from Parts A and B, and the emerging data from Part C. However, for each of the cohorts the doses will not exceed the doses previously tested in Part A and Part B. In addition, the increase from one dose level to the next dose level within the same cohort or between cohorts will not be more than 3-fold.

[b] Doses have now been selected as per protocol based on data from all patients of Cohort C1 who have completed the Main Treatment Period (n=12).

Part C may commence after the first 3 cohorts of Part B have been completed, providing there is sufficient appropriate data available (safety and tolerability, PK, and PD) to enable determination of dose levels.

The following table provides an overview of the doses (µg) planned to be adminstered in Part C [redacted]

[redacted]							
[redacted]							
Part C Cohort						C1[b] 20 (dose 1) 40 (dose 2)	C2[b] fixed dose of 10 (dose 1) fixed dose of 20 (dose 2)

[redacted]

[b] Part C may commence after completion of the first 3 cohorts of Part B.

The follow-up visit will take place on Day 37 (±2 days) only for patients not entering the extension period. The Sponsor is prolonging the treatment period of each of the Part C cohorts (patients with HP) with an open label extension of 2 months. Eligible patients will therefore remain treated with AZP-3601 and will not perform the follow-up visit. This extension period will allow collection of efficacy and safety data over a longer-term period (3 months) and treatment protocol is adressed in the current protocol amendment.

Before proceeding to the second cohort, the SRC will review the data of the first cohort. Review will be performed on safety and tolerability data, available PD data (with at least serum and urinary calcium, serum phosphate, and number of patients achieving reduction/elimination in calcium and active vitamin D supplements), and available PK data. In addition, the safety data of each of the cohorts will be reviewed on a regular basis during the treatment period.

Although this is an ascending dose study, a lower dose may be administered in the second cohort based on the safety, tolerability, or available PD and plasma PK results of the first cohort. Also, the same dose may be tested or an intermediate dose may be tested to gain more information on safety, tolerability, PD, and/or PK.

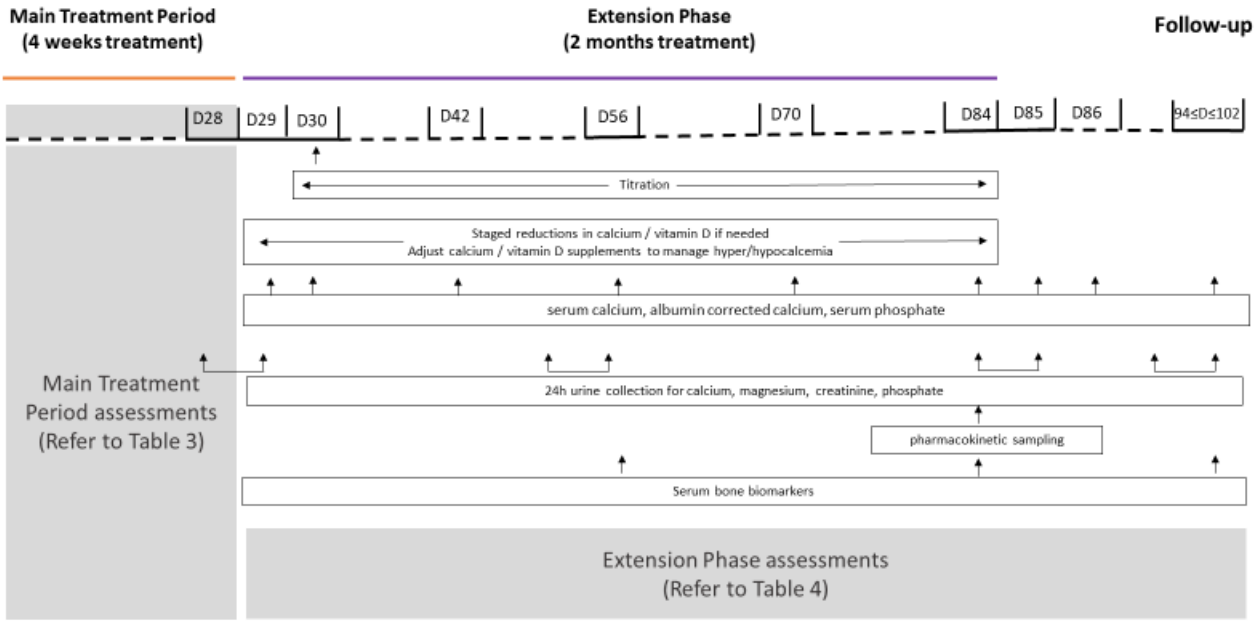
There will be an interval of at least 7 days between the last dose in the first cohort and the first dose in the second cohort. Subjects included in the first cohort cannot participate in the second cohort.

Part C, Extension Phase

Patients completing the 4 weeks Main Treatment Period of Part C, will be offered to enter a 2-months open label treatment extension phase. For patients willing to enter the extension phase, an ICF should be signed on Day 28 at the latest.
Patients will have to complete study assessments up to Day 28, as described in Table 3 and from Day 29 onwards, as described in Table 4.

Patients who will not participate to the Extension phase will have to complete study assessments as described in Table 3.

The overall study schematic for the Extension Phase of Part C, is presented hereafter (for more details, please refer to the Schedule of Assessments – Part C, Extension Phase in Table 4



The 2 month open label treatment extension phase will start immediately following Day 28 visit of the Main treatment period. Patients will receive AZP-3601 for 56 days (2 months) as daily sc injections from Day 29 onwards (with rotation of injection sites each day of administration).

The goal is to optimize AZP-3601 dosing across a dose range while doses of oral calcium and active vitamin D are as low as safely possible and albumin-corrected serum calcium is maintained within the target range of 7.8 to 9.0 mg/dL (1.95 to 2.25 mmol/L) together with an optimal control of the symptoms of hypoparathyroidism.

For patients who are taking minimal or no supplemental calcium (≤500 mg/day) and no vitamin D on Day 28, the AZP-3601 dose from the previous 14 days of treatment (Part C, Main Treatment Period) can be maintained and adjusted when needed during the Extension Phase.
For patients who are still taking active vitamin D and/or more than 500 mg/day of oral calcium on Day 28, a progressive reduction of supplements will be carried out while increasing the dose of AZP-3601.
On Day 29 onwards, patients will continue on the same dose of AZP-3601 as on Day 28, then individual titration of AZP-3601 may start as early as Day 30 and patients may have their dose of AZP-3601 adjusted at any time during the Extension Phase.
Patients may have their AZP-3601 dose increased, as previously defined, with the goal of achieving or maintaining albumin-corrected serum calcium in the target range of 7.8 to 9.0 mg/dL (1.95 to 2.25 mmol/L).

The AZP-3601 dose may be adjusted downward at anytime as needed to maintain albumin-corrected serum calcium within the target range or for any safety concerns.

Once patients achieve a stable albumin-corrected serum calcium with the minimum doses of supplements, they will be maintained at that dose of AZP-3601.

Patients will have their serum calcium/Albumin levels measured within 5 days after any adjustment of AZP-3601 and any other time at the discretion of the investigator. The investigator will be free to perform any other serum or urine test if needed.

In addition, there may be additional and unscheduled checks for serum calcium and phosphate at the discretion of the investigator.

At any time during the study, hypercalcemia and hypocalcemia will be managed by adjustment in active vitamin D and/or oral calcium supplementation. Adjustments will be based on laboratory values including albumin-corrected serum calcium and serum phosphate as well as on symptoms and will be performed at the Investigator's judgment. As a general guidance, adjustments should be performed when calcium values are outside the target range of 7.8 to 9.0 mg/dL, ie, 1.95 to 2.25 mmol/L.

A separate titration guideline to help the investigator and to facilitate a standardized approach to dose adjustment, will be provided to the clinical site (refer to Appendix 8.3).

Study Schedule*

[redacted]

Screening/Optimization : **Part C**: between Day -56 (±2 days) and Day -1. During the optimization period, doses of oral calcium and active vitamin D will be adjusted to ensure a close albumin-corrected serum calcium baseline for all subjects. In addition, any serum 25-hydroxy vitamin D (native vitamin D) and/or magnesium deficiencies will also be corrected during this optimization period.
On Day -1, at the end of the optimization period, subjects will visit the clinical site and will be evaluated for selected baseline measurements.

Treatment period [redacted]

Part C:

Main Treatment Period

On Day 1, the subjects will complete the baseline measurements and receive the first dose of AZP-3601 at the clinical site. Subjects will leave the clinical site following completion of all study assessments.

Subjects will return to the clinical site for additional visits on Day 14, Day 15, Day 16, Day 28/Early Termination (ET), and Day 29.

Serum calcium and phosphate blood samples will also be taken on Day 3 (±1 day), Day 5 (±1 day), Day 8 (±1 day), Day 11 (±1 day), Day 21 (±1 day), and Day 30. In addition, there may be additional and unscheduled checks for serum calcium and phosphate at the discretion of the Investigator. After the last study drug administration, if subjects are not entering the extension period, they will be instructed to resume their prestudy calcium and active vitamin D treatment regimen and doses based on assessments performed on Day 28/ET to Day 30.

Extension Phase

Extension phase will start immediately following Day 28 visit. On Days 29 onwards, patients will continue on the same dose of AZP-3601 as on Day 28, then individual titration of AZP-3601 may start as early as Day 30.

Patients will return to the clinical site for additional visits on Day 56 (±4 day), Day 84/ET (±4 day), and Day 85 (Day 84 + 1 day).

Serum calcium and phosphate blood samples will also be taken on Day 42 (±4 day), Day 70 (±4 day), and Day 86 (Day 84 + 2 days). In addition, there may be additional and unscheduled checks for serum calcium and phosphate at the discretion of the Investigator.

Patients will have their serum calcium/albumin levels measured within 5 days after any adjustment of AZP-3601 or any other time at the discretion of the investigator. The investigator will be free to perform any serum or urine test if needed.
After the last study drug administration, the patients will be instructed to resume their prestudy calcium and active vitamin D treatment regimen and doses based on assessments performed on Day 84 (±4 day) to Day 86 (Day 84 + 2 days).

Follow-up [redacted]

Part C: For patients not entering the extension phase, the follow-up visit will be on Day 37 (±2 days). For patients entering the extension phase, the follow-up visit will be on Day 98 (±4 days)

** For each study part, the planned treatment period, day of discharge, and follow-up period may be adapted depending on emerging study results.*

Subjects/Patients

[redacted]

Part C : Approximately 24 male or female subjects with HP who are on treatment with oral calcium and active vitamin D

Diagnosis and Main Criteria for Inclusion

[redacted]

Part C

Status : - History of HP for ≥12 months at the time of screening with documentation of two concomitant measurements of albumin-corrected serum calcium and parathyroid hormone (PTH), including:
1) A historical (≥12 months) laboratory analysis showing:
   - low serum PTH (<20 pg/mL), and,
   - low albumin-corrected serum calcium or low ionized serum calcium (below the lower limit of normal value of the laboratory).
2) A recent (<12 months) laboratory analysis showing :
   - low PTH (< 20pg/mL), and,
   - albumin-corrected serum calcium either:
     - below the lower limit of normal value of the laboratory, or,

- within the normal range of the laboratory under standard of care

If historical laboratory analysis (≥12 months) is not available, an additional recent concomitant laboratory measurement is required (with a minimum of 3 weeks testing interval).

- Requirement for therapy with calcitriol ≥0.25 µg per day or alphacalcidol ≥0.50 µg per day (both are active vitamin D supplements), and requirement for supplemental oral calcium treatment ≥1000 mg per day over and above normal dietary calcium intake prior to baseline measurements.
- Part C (Extension phase): Patients entering the extension phase need to have completed the Day 28 visit of the Main treatment period and sign the ICF before entering the extension phase.

Sex : Male or female
Age : 18 to 75 years, inclusive, at screening

Study Drug

Active medication

Drug product : AZP-3601
Activity : PTH analog
In development for : HP
Strength : 40 µg of AZP-3601 per vial
Dosage form : Powder for solution for injection
Route of administration : sc abdominal injection (with rotation of injection sites every dosing day for Parts B and C)
Manufacturer : NUVISAN GmbH, Neu-Ulm, Germany

Active medication (additional batch for Part C)

Drug product : AZP-3601
Activity : PTH analog
In development for : HP
Strength : 100 µg of AZP-3601 per vial *
Dosage form : Powder for solution for injection
Route of administration : sc abdominal injection (with rotation of injection sites every dosing day)
Manufacturer : NUVISAN GmbH, Neu-Ulm, Germany

[redacted]

Variables*

Safety and Tolerability

Variables : Adverse events, clinical laboratory (clinical chemistry, hematology, coagulation, and urinalysis), vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature), 12-lead electrocardiogram and time-matched with PK sampling ([redacted] Part C), continuous cardiac monitoring ([redacted], body weight, physical examination (full or abbreviated), injection site reaction, and presence of antidrug antibodies (ADA) in plasma (ADA for Part C only)

For hypocalcemia and hypercalcemia events, time of onset, amount of supplements administered, and timing will be recorded.

PK Variables : - Plasma AZP-3601 concentrations
- Plasma PK parameters estimated using noncompartmental analysis, as appropriate.

[redacted]

Day 1 of Part [redacted] C: C_{max}, t_{max}, AUC_{0-t}, AUC_{0-12}, and AUC_{0-24}.

[redacted] Day 28 of Part C (Main treatment period) and Day 84 of Part C (Extension phase): C_{max}, C_{trough}, C_{min}, t_{max}, k_{el}, $t_{1/2}$, AUC_{0-12}, AUC_{0-24}, CL_{ss}/F, V_z/F, and R_{ac}

PD and Other Variables : Parts [redacted] C:
- Levels of serum total calcium, albumin-corrected serum calcium, and serum phosphate.
- 24-hour urine calcium, phosphate, renal clearance of calcium and phosphate, fractional excretion (FECa) of calcium and phosphate, [redacted] magnesium, renal tubular maximum reabsorption of phosphate/glomerular filtration rate (TMP/GFR).
- Endogenous serum PTH(1-84) levels.

: Parts [redacted] C only:
- Bone turnover biomarkers (serum bone-specific alkaline phosphatase [BSAP], serum carboxy-terminal telopeptide of type I collagen [s-CTx], serum procollagen type 1 amino-terminal propeptide [P1NP], and serum osteocalcin).
- Serum magnesium.
- Serum 25-hydroxy vitamin D and serum 1,25-dihydroxy vitamin D.

Part C only:
- Reduction in daily dose of calcium and active vitamin D supplementation (number of patients achieving a reduction of 50% and more in daily doses of calcium and active vitamin D supplementation at the end of the treatment period will be calculated).
- EQ-5D questionnaire and short form health survey 36 (SF-36) questionnaire.
- Bone mineral density as assessed by DXA

** The timing, type, and number of safety, PK, PD, and additional assessments may be changed during the study depending on emerging study results.*

Statistical Methods

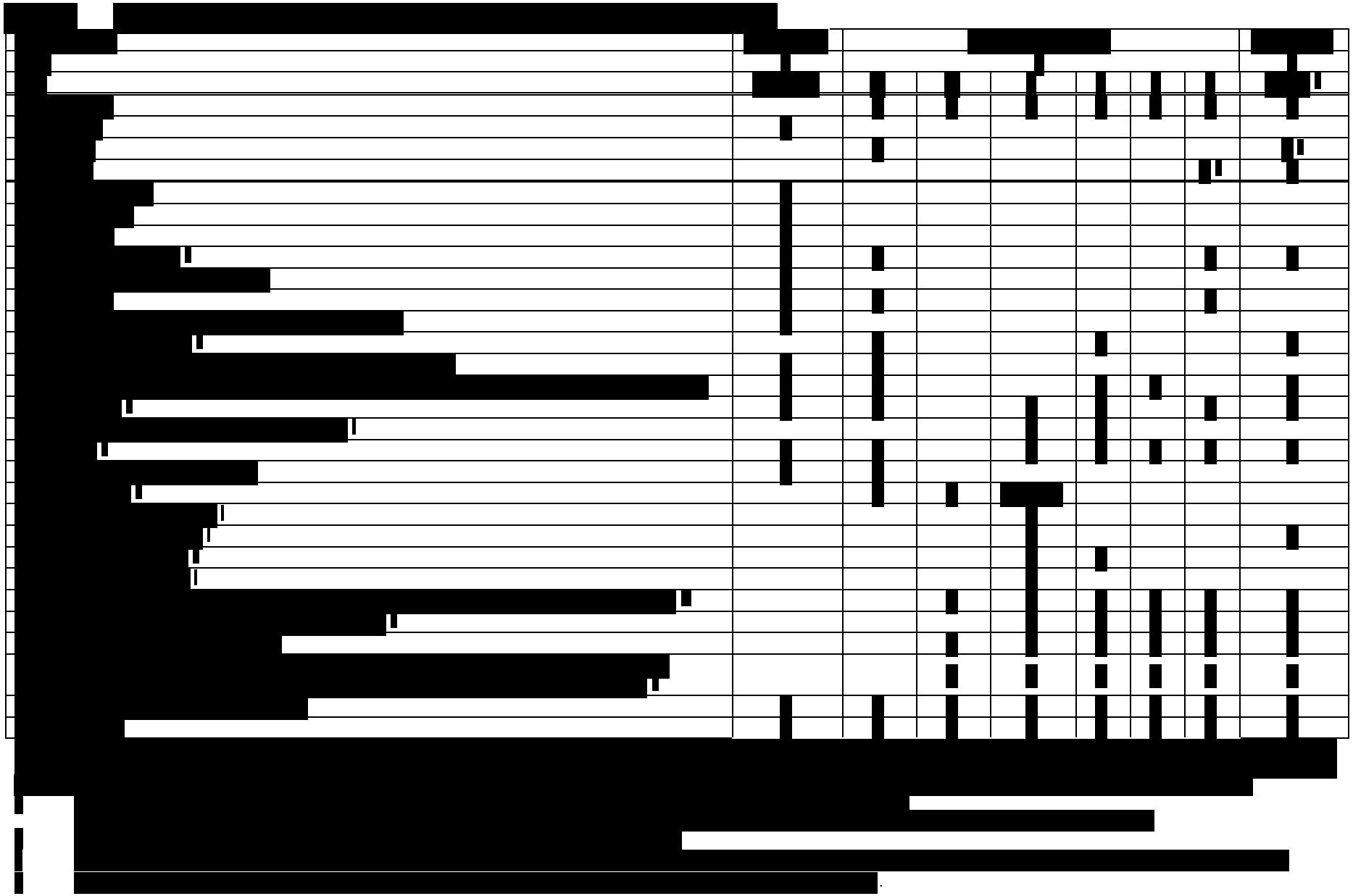
Sample Size Calculation : The sample size and design for each part is based on the desire to obtain adequate safety, tolerability, PK, and PD data to achieve the objectives of the study while exposing as few subjects as possible to the investigational product and study procedures. This sample is typical for a FIH study. Any p-values to be calculated according to the statistical analysis plan will be interpreted in the perspective of the exploratory character of this study.

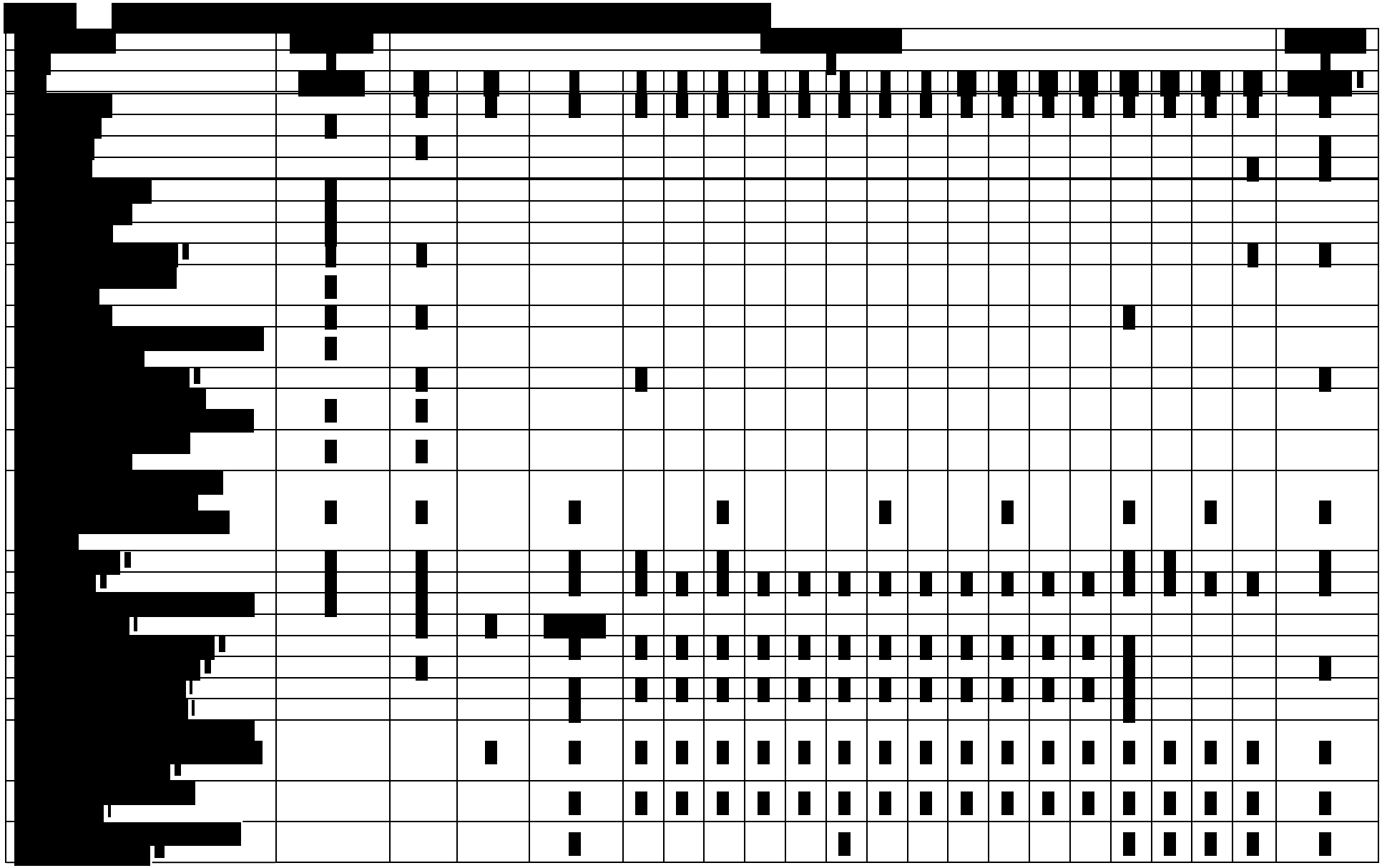
Safety : Descriptive statistics

PK : Descriptive statistics for all relevant PK parameters: n, mean, SD, minimum, median, maximum, geometric mean, and CV%; analysis of variance on C_{max} and AUC parameters to determine dose-proportionality

PD and Additional : Descriptive statistics. [redacted]

[redacted] Further details will be provided in the statistical analysis plan.





[redacted]

Table 3 Schedule of Assessments – Part C (MAD Part in Patients with HP – Main Treatment Period)

Assessment	Screening/Optimization						Main Treatment Period (4 weeks treatment)												Follow-up
(Week) Day	(-8)	(-6) [a,b]	(-4) [a,b]	(-2) [a,b]	-4 [b]	-1	1	3 [b]	5 [b]	8 [b]	11 [b]	14	15	16	21 [b]	28/ ET	29	30 [b]	37
Visit Window (days)	±2	±2	±2	±2	±1			±1	±1	±1	±1				±1				±2
Informed Consent	X															X [p]			
Medical History	X																		
Demography	X																		
Dispensing and Training of Diary							X												
Completion of Diary							X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination [c]	F						A					A		A		F	A		A
Body Weight and Height	X															X [q]			
Serum Pregnancy Test (Females of childbearing potential Only)	X					X						X				X			
Clinical Laboratory (Clinical Chemistry, Hematology, Coagulation, and Urinalysis) (Fasted)	X					X										X			X
12-Lead ECG [d]	X																		
Vital Signs [e]	X					X	X					X	X			X	X		X
SARS-CoV-2 test	X					X													
Inclusion and Exclusion Criteria	X					X													
Study Drug Administration [f]							X	X	X	X	X	X	X	X	X	X			
Drug Accountability												X				X [r]			
Blood Sampling for ADA [g]						X										X			X
Injection Site Reaction [h]							X					X	X	X		X	X		X
Blood Sampling for PK [i]							X					X				X			
Blood Sampling: Total Calcium, Albumin-Corrected Calcium, and Phosphate in Serum [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Active Vitamin D and Oral Calcium Supplementation Adjustment [k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Magnesium and Native Vitamin D Supplementation Adjustment, if needed	X	X	X	X	X	X													
Blood Sampling: Endogenous Serum PTH(1-84)	X					X						X				X			X
Blood Sampling: Bone Turnover Biomarkers [l]	X					X						X				X			X

Assessment	Screening/Optimization						Main Treatment Period (4 weeks treatment)												Follow-up
(Week) Day	(-8)	(-6) [a,b]	(-4) [a,b]	(-2) [a,b]	-4 [b]	-1	1	3 [b]	5 [b]	8 [b]	11 [b]	14	15	16	21 [b]	28/ ET	29	30 [b]	37
Visit Window (days)	±2	±2	±2	±2	±1			±1	±1	±1	±1				±1				±2
Blood Sampling: 25-Hydroxy Vitamin D (Native Vitamin D) and 1,25-Dihydroxy Vitamin D in Serum	X					X										X			
Blood Sampling: Serum Magnesium	X					X										X			
Blood Sampling: Serum Creatinine [o]						X	X					X				X	X		X
24-Hour Urine Collection: Calcium, Phosphate, Creatinine (for Calculation of FECa of Calcium and Phosphate and for Calculation of TMP/GFR), and Magnesium [m]							X					X					X		X
EQ-5D questionnaire						X										X			
SF-36 questionnaire						X										X			
DXA (bone mineral density) [n]							X												
Previous and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

A=abbreviated physical examination; ADA=antidrug antibodies; AE=adverse event; ECG=electrocardiogram; F=full physical examination; FECa=fractional excretion; PD=pharmacodynamic(s); PK=pharmacokinetic(s); PTH=parathyroid hormone; sc=subcutaneous; SF-36=short form health survey 36; TMP/GFR=tubular maximum reabsorption of phosphate/glomerular filtration rate; DXA=dual-energy x-ray absorptiometry

a Weeks -6, -4, and -2 visits are mandatory but may be combined when albumin-corrected serum calcium is within the target range.

b These visits are mandatory. As an alternative, these visits may be performed off-site; for instance, blood sampling may be performed at a local laboratory or at home by a study nurse. In addition, during the optimization period, there may be optional weekly visits.

c A full physical examination will be done at screening, and on Day 28 (predose). An abbreviated physical examination will be done on Days 1, 14, and 16 (at predose), and 29, and at follow-up. Unscheduled symptom-directed physical examinations may be conducted at any time per the Investigator's discretion.

d Single 12-lead ECG: at screening. The ECG will be recorded after the subject has been resting for at least 5 minutes in the supine position.

e Supine systolic and diastolic blood pressure, pulse rate, and body temperature: at screening, on Day -1, on Days 1, 14, 15, and 28 at predose, on Day 29, and at follow-up. Vital signs will be recorded after the subject has been resting for at least 5 minutes in the supine position.

f Subjects in Part C will receive AZP-3601 for 28 days as daily sc abdominal injections (with rotation of injection sites every dosing day). During the study visit the injection will be performed at the clinical site.

g Blood sampling for ADA: on Day -1, on Day 28, and at follow-up. All samples will be analyzed. In case of positive ADA, patients will be monitored until the levels return to normal.

h Injection site reaction: postdose on Day 1, predose and 1 hour postdose (when dosing) on Days 14, 15, 16, and 28, on Day 29, and at follow-up.

i Blood sampling for PK of AZP-3601 in plasma: serial samplings on Days 1, 14, and 28 (predose, 5min, 10min, 20min, 30min, 1 hour and 2 hours post dose).

j Serial sampling on Days 1, 14, and 28 (predose, 2 hours and 6 hours post dose). Samples will be taken fasting and pre-dose, except when profile where pre- and post-doses are taken

k At any time during the study, hypercalcemia and hypocalcemia will be managed by adjustment in active vitamin D and/or oral calcium supplementation. Adjustments will be based on laboratory values including albumin-corrected serum calcium and serum phosphate as well as on symptoms and will be performed at the Investigator's judgment.

l Bone turnover biomarkers include serum bone-specific alkaline phosphatase, serum carboxy-terminal telopeptide of type I collagen, serum procollagen type 1 amino-terminal propeptide, and serum osteocalcin.

m	The schedule of assessment indicates the end of collection day of each 24h collection.Refer to Section 3.5.1.3.2 and Figure 4 for more details.
n	DXA scans can be obtained within 2 weeks prior to the Day 1 visit
o	Sample will be taken predose and fasting
p	For patients willing to enter the extension phase, an ICF should be signed on Day 28 at the latest
q	Only weight is measured at Day 28
r	Day 28: Dispense study drug to the patients participating to the extension phase

Table 4 Schedule of Assessments - Part C Extension Phase

Assessment		Extension Phase (2 months treatment) [d]						Follow-up
Day (Month)	**D29-D30 [p]**	**42 [b]**	**56 (Month 1)**	**70 [b]**	**84/Early termination (Month 2)**	**85 (D84+1d)**	**86 [b] D84+2d)**	**98**
Visit Window (days)		**±4**	**±4**	**±4**	**±4**			**±4**
Informed Consent [a]								
Completion of Diary		X	X	X	X	X	X	X
Physical Examination [c]			A		F	A		A
Body Weight					X			
Serum Pregnancy Test (Females of childbearing potential Only)			X		X			
Clinical Laboratory (Clinical Chemistry, Hematology, Coagulation, and Urinalysis) (Fasted)			X		X			X
Vital Signs [e]			X		X	X		X
SARS-CoV-2 test [m]								
Study Drug Administration [f]		X	X	X	X			
Drug Accountability [o]			X		X			
Blood Sampling for ADA [g]			X		X			X
Injection Site Reaction [h]			X		X	X		X
Blood Sampling for PK [r]					X			
Blood Sampling: Total Calcium, Albumin Corrected Calcium, and Phosphate in Serum [i]		X	X	X	X	X	X	X
Active Vitamin D and Oral Calcium Supplementation Adjustment [j]		X	X	X	X	X	X	X
Blood Sampling: Endogenous Serum PTH(1-84)			X		X			X
Blood Sampling: Bone Turnover Biomarkers [k]			X		X			X
Blood Sampling: 25Hydroxy Vitamin D (Native Vitamin D) and 1,25Dihydroxy Vitamin D in Serum			X		X			
Blood Sampling: Serum Magnesium			X		X			
Blood Sampling: Serum Creatinine [n]			X		X	X		X
24-Hour Urine Collection: Calcium, Phosphate, Creatinine (for Calculation of FECa of Calcium and Phosphate and for Calculation of TMP/GFR), and Magnesium [l]			X			X		X
EQ-5D questionnaire					X			
SF-36 questionnaire					X			
DXA (bone mineral density) [q]					X			
Previous and Concomitant Medication		X	X	X	X	X	X	X
AE Monitoring		X	X	X	X	X	X	X

A=abbreviated physical examination; ADA=antidrug antibodies; AE=adverse event; ECG=electrocardiogram; F=full physical examination; FECa=fractional excretion; PD=pharmacodynamic(s); PK=pharmacokinetic(s); PTH=parathyroid hormone; sc=subcutaneous; SF-36=short form health survey 36; TMP/GFR=tubular maximum reabsorption of phosphate/glomerular filtration rate; DXA=dual-energy x-ray absorptiometry

a For patients willing to enter the extension phase, an ICF should be signed on Day 28 at the latest

b These visits are mandatory. As an alternative, these visits may be performed off-site; for instance, blood sampling may be performed at a local laboratory or at home by a study nurse.

c F=Full physical examination. A=Abbreviated examination. Physical Examination are done predose at visits when there is a dosing. Unscheduled symptom-directed physical examinations may be conducted at any time per the Investigator's discretion.

d The 2 month open label treatment extension phase will start immediately following Day 28 visit of the Main treatment period. Patients will complete study assessments up to Day 28 as described in Table 3, and from Day 29 onwards as described in Table 4.

e Supine systolic and diastolic blood pressure, pulse rate, and body temperature. Vital signs will be recorded after the subject has been resting for at least 5 minutes in the supine position. Vital Signs are done predose at visits when there is a dosing.

f Subjects will receive AZP-3601 for 56 days (2 months), as daily sc abdominal injections (with rotation of injection sites every day of administration) from Day 29 onwards. On Day 29 onwards, patients will continue on the same dose of AZP-3601 as on Day 28 then individual titration may start as early as Day 30, and patients may have their dose of AZP-3601 adjusted at any time during the extension phase.

During study visits, the injection will be performed at the clinical site.

g All blood sampling for ADA will be analyzed. In case of positive ADA, patients will be monitored until the levels return to normal.

h Injection site reaction: predose and 1 hour postdose when there is a dosing

i Serial sampling on Days 56 and 84 (predose, 2 hours and 6 hours postdose). Samples will be taken fasting and pre-dose, except when profile where pre- and post-doses are taken.

j At any time during the study, hypercalcemia and hypocalcemia will be managed by adjustment in active vitamin D and/or oral calcium supplementation. Adjustments will be based on laboratory values including albumin-corrected serum calcium and serum phosphate as well as on symptoms and will be performed at the Investigator's judgment.

k Bone turnover biomarkers include serum bone-specific alkaline phosphatase, serum carboxy-terminal telopeptide of type I collagen, serum procollagen type 1 amino-terminal propeptide, and serum osteocalcin.

l The schedule of assessment indicates the end of collection day of each 24h collection. Refer to Section 3.5.1.3.2 and Figure 4 for more details.

m Testing may be performed at the discretion of the Investigator. Testing will be performed using a country registered detection test

n Samples will be taken predose and fasting

o Dispense the study drug to the patients on Day 28. Study drug return/dispense on Day 56 and Study drug return on Day 84

p On Day 29 and Day 30, the subjects will follow the same assessments than ones listed in Table 3, except:
- Blood Sampling: Total Calcium/Albumin- Corrected Calcium/Phosphate and Creatinine in Serum, taken predose in addition to fasting
- Physical Exam and Vital signs at predose
- Injection site reaction at pre-dose and at 1-hour postdose.

q DXA scans can be obtained within 2 weeks prior to the end of the extension phase visit (Day 84 visit).

r Blood sampling for PK of AZP-3601 in plasma: serial samplings on Day 84 (predose, 5min, 10min, 20min, 30min, 1 hour and 2 hours post dose).