Statistical Analysis Plan

Sponsor:	Amolyt Pharma
Protocol No:	AZP-3601-CLI-001
Protocol 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
PRA Project ID:	AZP20005-20005X
Version Date:	26-Aug-2022 (SAP V3)

1.0 Approvals

The undersigned have approved this Statistical Analysis Plan for use in this study.

Name of Sponsor Representative / Title:	Soraya Allas, MD, PhD / VP Clinical Development and Regulatory Affairs, Amolyt Pharma
Signature of Sponsor Representative / Date:	[redacted] 30/08/2022
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Signature of Author / Date:	[redacted]

2.0 Table of Contents

3.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under Amolyt Pharma Protocol AZP-3601-CLI-001. This SAP covers [redacted] and the analyses to be performed for Part C (study conducted in patients with hypoparathyroidism).

This SAP should be read in conjunction with the study protocol. This version of the SAP has been developed using the global protocol version 5.0 dated 12-May-2021, and the country specific protocol amendments dated 17-Mar-2021 for Netherlands, 8-Apr-2022 for France (Version 7.0) and 11-Apr-2022 for Hungary and Spain (Version 7.0) (including all amendments up to this protocol date).

An approved and signed SAP is a requirement for database lock. An approved SAP is also required for unblinding of the study treatments.

This SAP only covers the results that will be processed by the PRA Early Development Services (EDS) Biostatistics Department.

PRA EDS will perform the pharmacokinetic (PK), pharmacodynamic (PD), and safety and tolerability evaluation.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be identified. Any post-hoc or unplanned analyses, or significant changes from the planned analysis in this SAP performed to provide results for inclusion in the clinical study report (CSR) but not included in this SAP, will be clearly identified in the CSR. Changes to planned analyses do not require an updated SAP but should be included in the CSR if significant.

4.0 Changes from Previous Version of Approved SAP

Version 2.0:

- Overall changes based on updated versions of the protocol.
- Inclusion of the analyses related to Part C (Main treatment period and Extension phase)

Version 3.0:

- Inclusion of additional PK samplings of AZP-3601 in plasma at D84, during the Extension phase of part C according to protocol version 7.0
- Added listing of SF-36 Questionnaire - Physical and Mental Component Score (Part C only)

5.0 Study Objectives

5.1 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 hypoparathyroidism (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

5.2 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)

5.3 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)

6.0 Study Design

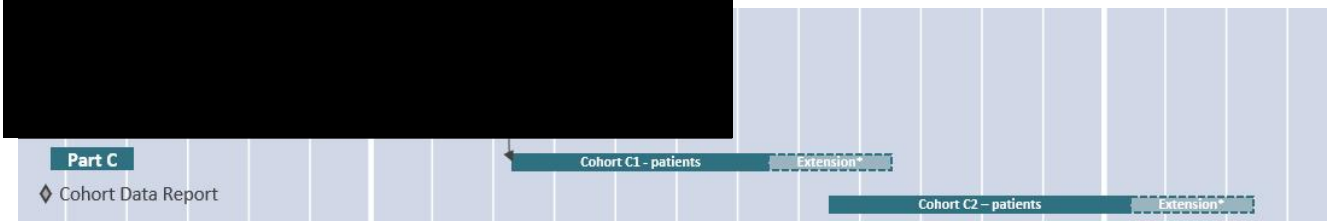
This is a first-in-human (FIH) study in healthy subjects followed by a study in patients with HP combined in a single protocol. [redacted] Part B will be followed by a MAD part in patients with HP who will receive AZP3601 for 4 weeks (Part C).

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]

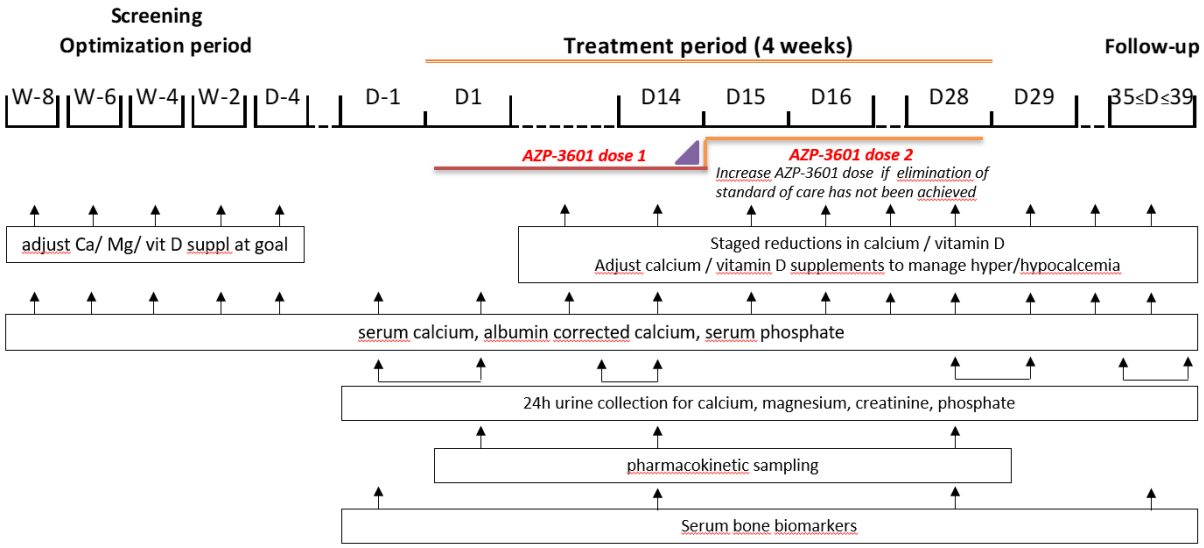
[redacted]

Part C (MAD part in patients with HP)

Part C will be an open-label MAD study in male or female patients 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 figure below illustrates the study design for Part C for the Main Treatment Period.



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) and therefore ensuring a common baseline for all patients.

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

During the main 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). 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. The days of dose reduction of supplements may change based on data from Part B; they may be advanced or delayed based on (but not limited to) when the PD steady state is observed.

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). 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.

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

Cohort C1: sc doses of 20 µg AZP-3601 (n=12) qd from Day 1 to Day 28 (dose of AZP-3601 may be increased to 40 µg from Day 14 onwards)

Cohort C2: sc doses of a fixed dose up to 40[a] µg AZP-3601 (n=12) qd from Day 1 to Day 28 (dose of AZP-3601 may be increased at a fixed dose up to 60 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.

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]								
Part C Cohort							C1[b] 20 (dose 1) 40 (dose 2)	C2[b] fixed dose up to 40 (dose 1) fixed dose up to 60 (dose 2)

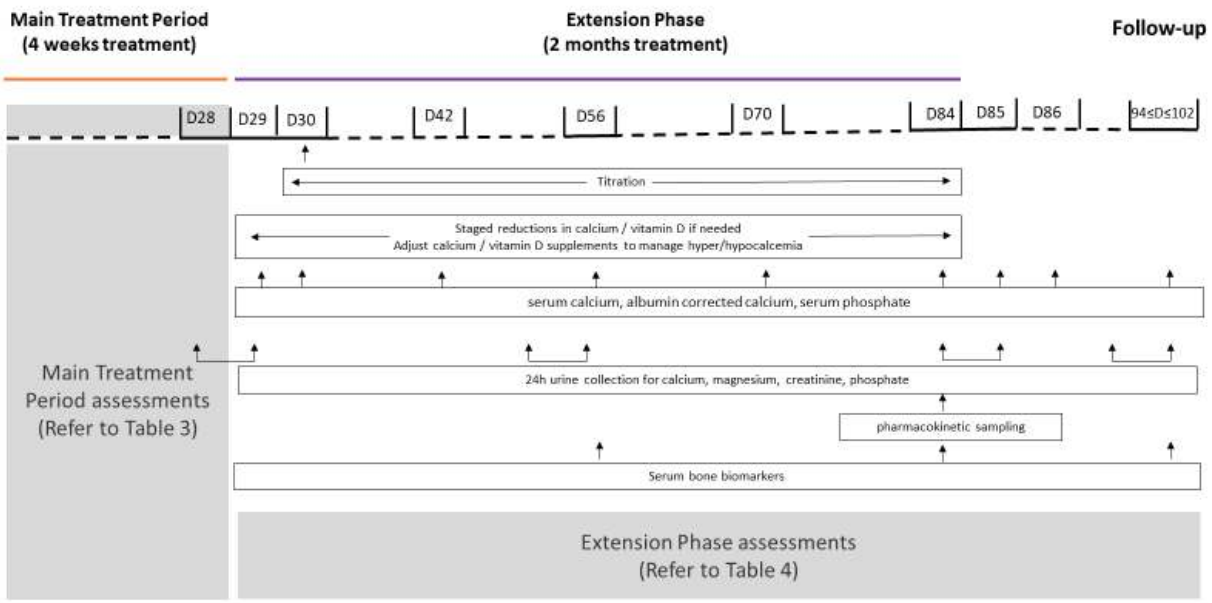
[a] Part B may commence following completion of the first 3 cohorts of Part A.
[b] Part C may commence after completion of the first 3 cohorts of Part B.

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. Patients included in the first cohort cannot participate in the second cohort.

Part C, Extension Phase

The figure below illustrates the study design for Part C for the Extension Phase.



Patients completing the 4 weeks Main Treatment Period of Part C, will be offered to enter a 2-month open label treatment extension phase. For patients willing to enter the extension phase, an informed consent form (ICF) should be signed on Day 28 at the latest.

Patients will have to complete study assessments up to Day 28, as described in Schedule of Assessments Table 4 (in the Appendix 2) and from Day 29 onwards, as described in Table 5 (in the Appendix 2).

Patients who will not participate to the Extension phase will have to complete study assessments as described in Table 4 (in the Appendix 2).

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

defined in previous section, with the goal of achieving or maintaining albumin-corrected serum calcium in the target range of 7.8 to 9.0 mg/dL.

The AZP-3601 dose may be adjusted downward at any time 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. A separate titration guideline to help the investigator and to facilitate a standardized approach to dose adjustment, will be provided to the clinical site.

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.

6.1 Sample Size Considerations

This is an exploratory trial for which no formal statistical hypothesis testing will be performed and therefore no formal sample size calculations have been done. The sample size is based on the desire to obtain adequate safety, tolerability, PK and PD data and is considered sufficient 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 SAP will be interpreted in the perspective of the exploratory character of this study.

6.2 Randomization

[redacted]

[redacted]

[redacted]

[redacted]

Part C is not randomized. All patients will receive AZP-3601 and no placebo will be administered. patients will be assigned to a cohort based on their availability. After obtaining written informed consent, patients will be screened according to the inclusion and exclusion criteria. Patients will be assigned unique patient numbers allocated in ascending order within the clinical site, that identify the study site and the individual subject. The patient number will be as follows: XXX-YYY, with XXX for country and site number, and YYY for patient counter. Any replacement patient will receive the number of the patient to be replaced, increased by 500 (thus XXX-501 as replacement for XXX-001).

7.0 Overview of Planned Analysis

7.1 Changes from Protocol

The PK parameter AUC_{0-6} will be provided whereas AUC_{0-12} and AUC_{0-24} will not be provided, because the drug is expected to eliminate quickly and because of the scheduled timepoints of PK assessments.

The PK parameter AUC_{0-inf} will be calculated at Day 1 for [redacted] C, therefore k_{el} will be also calculated at this timepoint as well as Adj R^2.

An additional analysis set (Enrolled Set) will be derived for Part C. The adverse events (AEs) in Part C will also be summarized for Enrolled Set.

7.2 Interim Analysis

[redacted]

[redacted]

For Par C, following completion of Cohort C1, an interim PK/PD report will be provided in a descriptive way, along with a dose escalation report (DER) describing the safety and tolerability, and available pharmacodynamic and pharmacokinetic data, to assist the SRC in dose escalation decision from Cohort C1 to Cohort C2.

The following PK/PD data will be included in the interim reports:

- PK: AZP-3601 plasma (pg/mL)
- PD: Serum Calcium (mg/dL)
- Serum Calcium corrected for Albumin (mg/dL)
- Serum Inorganic Phosphorus (mg/dL)
- Serum PTH, Intact (pg/mL)
- Urine Calcium excretion rate (estimated, mg/24h)
- Urinary fractional excretion of calcium (%)
- Urinary fractional excretion of inorganic phosphorus (%)
- ADAs

The interim safety reports will be generated by Principal Investigator (data is extracted from the system Oracle EDC).

7.3 Final Analysis

Draft TFLs will be provided [redacted] after the database lock of Part C. After Sponsor comments have been incorporated, the TFLs will be finalized and incorporated in the final CSR.

8.0 Definitions and General Analysis Methods

8.1 Analysis Data Presentation

8.1.1 Rounding

In listings, data will be presented with the same precision as the original data. Derived data will be rounded for presentation purposes.

For all summaries, except PK data summaries, the mean and median will be presented to one decimal place greater than the listed data, standard deviation (SD) to two greater than the listed data, and the minimum and maximum will be presented to the same number of decimal places as the listed data. Frequency percentages will be presented with one decimal.

For all PK data (i.e. concentrations and derived parameters) summaries, descriptive statistics will be presented as integers when values are ≥100 or presented with 3 significant figures when values are <100. The t_{max} values and descriptive statistics thereof will be reported with 2 decimals. Ratios will be presented with 1 decimal. The coefficient of variation (CV%) will be reported with 1 decimal.

P-values will be reported to four decimal places; p-value less than 0.0001 will be reported as p <0.0001.

8.1.2 Imputation

Unless otherwise noted, data will not be imputed. Exceptions are missing start and end times of adverse events (AEs), see Section 17.1.1, PK concentrations below lower limit of quantification (LLOQ), see Section 15.2, PTH(1-84) concentrations below LLOQ, see Section 16.2.2.1, and missing score in SF-36 Questionnaire, see section 16.1.5.

8.1.3 Descriptive Statistics

Unless otherwise indicated, continuous variables will be summarized with the following descriptive statistics: number of observations (n), (arithmetic) mean, SD, minimum (min) value, median, and maximum (max) value. For PK data, geometric mean and geometric CV will be presented in addition.

- Geometric mean = exp(m), where m is the arithmetic mean of the log-transformed data.

- Geometric CV (%): sqrt(exp(s*s)-1)*100, where s*s is the variance of the log-transformed data.

Categorical data will be summarized with frequencies and percentages. Percentages by categories will be based on the number of subjects exposed within a treatment.

For categorical data, the categories will be presented in the tables exactly as they appear in the electronic case report form (eCRF) / Database. No data manipulation will be done for presentation purposes.

8.1.4 Pooling

For each part, summary statistics will be calculated by treatment (and time point, if applicable).

8.1.5 Unscheduled Measurements

Unscheduled measurements will be included in the listings. Except for unscheduled measurements used for baseline, unscheduled measurements will be excluded from the descriptive statistics and statistical analysis.

8.2 Analysis Data Definitions

8.2.1 Baseline Definition

Unless otherwise stated, baseline for post-dose evaluations is defined as the last observation recorded before the first study drug administration in each study part. The last observation can be an unscheduled / repeated measurement. If a pre-treatment observation is missing then the screening value may be used. [redacted] Another exception is the baseline definition for the main PD analysis due to the potential batch effect (see Section 16.2.1).

8.2.2 Treatment/Subject Grouping

Label	Grouping
Study Drug	AZP-3601 and Placebo
Treatment	[redacted] Part C (MAD Part in Subjects with HP) multiple sc AZP-3601
Dose Level [a]	[redacted] Part C (MAD Part in patients with HP, Main Treatment Period) Cohort 1: 20µg qd from Day 1 to Day 28 (may be increased to 40 µg from Day 14 onwards) Cohort 2: 40µg qd from Day 1 to Day 28 (may be increased to 60 µg from Day 14 onwards) Part C (MAD in patients with HP, Extension Phase) 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 may change following review of the emerging data.

8.2.3 Common Variable Derivations

Variable	Definition/Calculation
Analysis Study Day (Prior to Dose)	Date of Measurement minus First Dose Date in each study part
Analysis Study Day (Post Dose)	Date of Measurement minus First Dose Date +1 in each study part
Scheduled time	Planned time of the assessment. Time in hours of the assessment relative to the planned time of the first drug administration in each study part
Actual Time	Actual time in hours calculated as the sampling data/time minus the date/time of the first drug administration in each study part
Change from Baseline	Post-dose observation minus baseline observation

8.2.4 ADaM Datasets and Metadata

The analysis datasets will be generated in accordance with Clinical Data Interchange Standard Consortium (CDISC) Analysis Data Model (ADaM) Version 2.1.

ADaM compliant datasets will be delivered to the Sponsor. A define.xml file version 2 with the corresponding metadata will be included. Analysis results metadata will be excluded.

At least the following datasets will be generated:

- Subject-level Analysis Dataset (ADSL)
- AEs Analysis Dataset (ADAE)

- Exposure Analysis Dataset (ADEX)
- Concomitant Medications Analysis Dataset (ADCM)
- Medical History Analysis Dataset (ADMH)
- Laboratory Analysis Dataset (ADLB)
- Vital Signs Analysis Dataset (ADVS)
- ECG Analysis Dataset (ADEG)
- PK Concentrations Analysis Dataset (ADPC)
- PK Parameters Analysis Dataset (ADPP)
- Pharmacodynamic Analysis Dataset (ADPD)

8.3 Software

The statistical analysis and reporting will be done using SAS® for Windows™ Version 9.4 or higher (SAS Institute, Inc.).

PK parameter calculations will primarily be done using Phoenix® WinNonlin® (WNL) version 8.1 or higher (Certara, Inc.). Additional PK computations may be performed in SAS®.

8.4 Statistical Methods

8.4.1 Statistical Outlier Determination

No statistical outlier analysis is planned.

8.4.2 Predetermined Covariates and Prognostic Factors

There are no predetermined covariates or prognostic factors.

8.4.3 Hypothesis Testing

No formal hypothesis testing will be done.

8.5 TFL Layout

Report layout will be according to the PRA EDS – International Council for Harmonisation (ICH) E3 compliant – CSR Template. The layout of TFLs will be according to the PRA EDS standards.

Format:

- Page size: A4
- Data in listings will be sorted by study part, subject number, [redacted] /cohort (for Part C) and time point.
- Data in tables will be sorted by study part, [redacted] /cohort (for Part C) and time point.
- Column titles will be in title case letters.
- All tables and listings will be in landscape format.

Study part refers to [redacted] 'Part C Main', and 'Part C Extension' if applicable: "Treatment" refers to placebo and various dose levels of study drug in the TFL.

Table, listing and figure shells will be provided together with the SAP.

9.0 Analysis Sets

Analyses	Safety Set	Pharmacokinetic Set	Pharmacodynamic Set	Enrolled Set (Part C only)
Disposition Summaries	✓	✓	✓	✓
Demographics	✓	✓	✓	✓
Baseline Characteristics	✓			
Medical History	✓			
Treatment Exposure	✓			
AE Summaries	✓			✓
CM Summaries	✓			
Other Safety Assessments	✓			
PK Concentrations Summaries		✓		
PK Parameters Summaries		✓		
PD Parameters Summaries			✓	

9.1 Safety Set

All subjects who have received at least 1 dose of AZP-3601 or placebo.

9.2 Pharmacokinetic Set

All subjects who have received at least 1 dose of AZP-3601 and provided sufficient bioanalytical assessment results to calculate reliable estimates of the PK parameters.

9.3 Pharmacodynamic Set

All subjects belonging to the safety set and for whom the PD data are considered to be sufficient and interpretable.

9.4 Enrolled Set (Part C only)

All patients who sign the informed consent form.

The table of “Disposition Summaries” will be presented from “All Subjects”, including summarizing the members of each analysis set. Moreover, all the listings will also be presented from “All Subjects”.

10.0 Subject Disposition

All disposition data will be listed.

[redacted] members of each analysis set will be presented. The number and percentage of subjects who withdrew from the study prematurely and a breakdown of the corresponding reasons for withdrawal will also be presented. Summaries will be reported by study part and treatment, as well as overall within each part.

11.0 Protocol Deviations and Violations

Protocol deviations will be collected and entered into the Clinical Trial Management System (CTMS) per clinical monitoring Standard Operating Procedures. From CTMS, protocol deviations will be pulled into study data tabulation model (SDTM). Important protocol deviation data will be listed by subject.

12.0 Demographic and Baseline Characteristics

12.1 Demographics

All demographic data will be listed by subject.

Subject demographics will be summarized descriptively for all subjects by study part and [redacted] /cohort (for Part C) as well as overall within each part. The summary will include the subjects' age (in years), gender, race (if available), ethnicity, weight (in kg), height (in cm), and body mass index (BMI) (in kg/m^2) at baseline. In addition, for Part C, the number and percentage of subjects will be summarized by age group '<45 years', '≥ 45 and <65 years' and '≥65 years'. Demographics will be summarized for the safety, PK, PD and enrolled sets if applicable.

12.2 Medical History and Disease under Study

Medical history will be listed by subject. Medical history data will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1.

Medical history will be summarized by system organ class (SOC) and preferred term (PT). The number and percentage of subjects will be presented by study part and [redacted] /cohort (for Part C).

For Part C, all the information related to disease under study will be listed by patient. A summary table will be provided for the duration (in years) and the etiology of hypoparathyroidism. Furthermore, menopause status will be summarized using the frequency of patients with or without menopause based on the total number of female patients, and using the time since menopause (years).

12.3 Other Baseline Characteristics

[redacted]

For Part C, a summary table and a listing will be provided for the following baseline values:

- Prescribed active vitamin D
- Prescribed active vitamin D in category (low, medium, high):
  - Calcitriol: low dose 0-0.25 µg/day, medium dose >0.25-0.5 µg/day, high dose >0.5 µg/day.
  - Alfacalcidiol: low dose 0-0.50 µg/day, medium dose >0.50-1.0 µg/day, high dose >1.0 µg/day
- Prescribed calcium
- Prescribed calcium in category:
  - 0-2000 mg/day
  - >2000 mg/day
- Serum total calcium
- Serum phosphate

- Albumin-adjusted serum calcium
- Serum 25-Hydroxyvitamin D
- Serum 1,25-Dihydroxyvitamin D
- 24-Hour urinary calcium (mg/24h)
- 24-Hour urinary calcium adjusted by creatinine
- FECa of calcium
- FECa of calcium in category
    - 0-2%
    - > 2%
- Bone turnover biomarkers
- e-GFR

The other baseline characteristics will be listed, including results of pregnancy tests, serology tests, drug and alcohol screen, SARS-CoV-2 Polymerase Chain Reaction (PCR) test and childbearing potential (Part C only).

13.0 Concomitant Medications

Prior and concomitant medications (drug treatment), categorized by standardized medication group according to the World Health Organization (WHO) Drug Dictionary (WHODrug Global B3 SEP2020), will be listed by subject. Medications with an end date prior to the first dose of study drug within each study part will be considered prior medications and will be identified in the listing. Any medication taken after the first dose of study drug, including those who started prior to the first dose of study and continued past that date will be considered concomitant medications. If a partial date allows a medication to be considered concomitant it will be categorized as such.

Concomitant medications (drug treatment) will be summarized by standardized medication group and [redacted] /cohort (for Part C) in each study part. The number and percentage of subjects using at least one medication within each standardized medication group will be presented by [redacted] /cohort (for Part C) in each study part.

In addition, prior and concomitant medications (non-drug treatment) will also be listed.

14.0 Treatment Compliance and Exposure

Exposure data of study drug, collected by CRF, will be listed by subject. In Part C, exposure data of study drug, collected by diary, will also be listed by subject. If applicable, date and time of meal intake and comments will be listed.

[redacted]

- [redacted]

For Part C, exposure data of study drug will be summarized by cohort for

- Dose exposure parameters separately by main treatment period and extension phase include:
    - Total actual dose received (µg) (Sum of all doses administered)
    - Number of doses received
    - Duration of exposure (in days) = last dose date - first dose date + 1
    - Dose Intensity (µg/day) = total actual dose received / duration of exposure
    - Relative Dose Intensity (ratio) = total actual dose received / total planned dose
- Dose increases during the main treatment period include:
    - Doses increases at Day 15 = Yes / No (doses at Day 15 versus doses at Day 1)

  - Doses increases after Day 15 = Yes / No (doses at Day 16 or later up to Day 28 versus doses at Day 1)
- Doses increases or decreases during the extension phase (versus actual dose at Day 28) include:
  - Number of patients with one increase only (without decrease)
  - Number of patients with at least two increases (without decrease)
  - Number of patients with one decrease only (without increase)
  - Number of patients with at least two decreases (without increase)
  - Number of patients with both increase and decrease
  - Number of patients with no change in dose

Study drug dispensing and returning will be listed by subject.

15.0 Pharmacokinetic Analyses

15.1 Pharmacokinetic Variables

15.1.1 Plasma Variables

15.1.1.1 Plasma PK Concentrations

- Plasma AZP-3601 concentrations

15.1.1.2 Plasma PK Parameters

- PK Parameters for AZP-3601 as defined in Table 1

Table 1 Plasma AZP-3601 PK Parameters

Parameter	[redacted]	[redacted] AND C Day 1	[redacted] AND PART C DAY 28 and DAY 84	Description	SAS Programming Notes
C_{max}		X	X	Maximum plasma concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units.	Cmax from WNL. C_{max} will be presented as “Cmax” in the TFL.
C_{trough}			X	Trough plasma concentration.	Derived in SAS C_{trough} will be presented as “Ctrough” in the TFL.
C_{min}			X	Minimum plasma concentration (predose concentration excluded)	Cmin from WNL. C_{min} will be presented as “Cmin” in the TFL.
t_{max}		X	X	Time to maximum plasma concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.	Tmax from WNL. t_{max} will be presented as “Tmax” in the TFL.
AUC_{0-t}		X		Area under the plasma concentration-time curve (time 0 to time of last quantifiable concentration).	AUClast from WNL. AUC_{0-t} will be presented as “AUClast” in the TFL.
AUC_{0-inf}		X		Area under the plasma concentration-time curve (time 0 to infinity). Calculated as: $AUC_{0-inf} = AUC_{0-t} + C_{last}/k_{el}$, where C_{last} is the observed concentration at time t, where t is the last point with a concentration above the lower limit of quantification. Percent extrapolation less than or equal to 20% and an adjusted r^2 greater than 0.80 are required to obtain a reliable AUC_{0-inf}.	AUCINF_obs from WNL. AUC_{0-inf} will be presented as “AUCinf” in the TFL. If $\%AUC_{extra}$ >20% then parameter is flagged. If Adj $R^2 \leq 0.80$ then parameter is

Parameter	[redacted]	[redacted] AND C Day 1	[redacted] AND PART C DAY 28 and DAY 84	Description	SAS Programming Notes
					flagged.
%AUC_{extra}				Percentage of estimated part for the calculation of AUCinf: Calculated as: $([AUC_{0\text{-}inf} – AUC_{0\text{-}t}]/ AUC_{0\text{-}inf})*100\%$.	AUC_%Extrap_obs from WNL. %AUC_{extra} will be presented as “AUC%extrap” in the TFL, and listed only.
$AUC_{0\text{-}6}$		X	X	Area under the plasma concentration-time curve from time zero up to 6 hours.	AUC0-6 from WNL AUC0-6 will be presented as “AUC(0-6)” in the TFL.
$AUC_{0\text{-}12}$			X	Area under the plasma concentration-time curve from time zero up to 12 hours.	AUC0-12 from WNL AUC0-12 will be presented as “AUC(0-12)” in the TFL.
$AUC_{0\text{-}24}$			X	Area under the plasma concentration-time curve from time zero up to 24 hours.	AUC0-24 from WNL AUC0-24 will be presented as “AUC(0-24)” in the TFL.
k_{el}		X		Terminal phase rate constant calculated by linear regression of the terminal log-linear portion of the concentration vs. time curve. Linear regression of at least three points and an adjusted r^2 greater than 0.80 are required to obtain a reliable k_{el}.	Lambda_z from WNL. k_{el} will be presented as “Kel” in the TFL, and listed only If Adj $R^2 \leq 0.80$ then parameter is flagged.
$t_{1/2}$		X		Terminal phase half-life expressed in time units. adjusted r^2 greater than 0.80 is required to obtain a reliable $t_{1/2}$.	HL_Lambda_z from WNL. $t_{1/2}$ will be presented as “t1/2” in the TFL. If Adj $R^2 \leq 0.80$ then parameter is flagged.

Parameter	[redacted]	[redacted] AND C Day 1	[redacted] AND PART C DAY 28 and DAY 84	Description	SAS Programming Notes
CL/F				Apparent oral clearance, calculated as dose/$AUC_{0\text{-}inf}$.	CL_F_obs from WNL. If $\%AUC_{extra}$ >20% or Adj $R^2 \leq 0.80$ then parameter is flagged.
CL_{ss}/F			X	Apparent oral clearance at steady state, calculated as dose/$AUC_{0\text{-}tau}$ where tau =6h (Parts B and C).	CLss_F from WNL CL_{ss}/F will be presented as "CLss/F" in the TFL.
Vz/F			X	Apparent volume of distribution at terminal phase, calculated as $(CL/F)/k_{el}$ (Part A), or as $(CL_{ss}/F)/k_{el}$ (Parts B and C).	VZ_F_obs from WNL. If $\%AUC_{extra}$ >20% or Adj $R^2 \leq 0.80$ then parameter is flagged.
R_{ac}			X	Accumulation ratio, based on $AUC_{0\text{-}tau}$ of Day 14 (Part B) or Day 28 (Part C) vs Day 1 where tau = 6h (Parts B and C).	Calculated in SAS. Rac will be presented as "Rac" in the TFL.
Adj R^2		X		Goodness of fit statistic for the log-linear terminal elimination phase of the concentration-time profile identified by least-squares linear regression and adjusted for the number of points (minimum of 3) used in the estimation of k_{el}.	"Rsq_adjusted" from WNL. Adj R^2 will be presented as "Adj R2" in the TFL and listed only.

Note: AUCs will be calculated using linear up / log down, expressed in units of concentration x time.

15.2 Pharmacokinetic Summaries

15.2.1 Pharmacokinetic Concentrations

All AZP-3601 plasma concentrations will be reported under PK population set with data handling of PK Data Set and PK Data Set Info (for information only). Under PK Data Set, analyses on the concentrations will be performed with values under LLOQ set as “BQL”. Under PK Data Set Info, AZP-3601 plasma concentration will include the concentrations extrapolated from the analyte response under the LLOQ (for information purpose); values under LLOQ will either be a “No peak” or an actual value between 0 and the LLOQ value (i.e. 50 pg/mL). The Inclusion of the informative PK concentrations ("No peak” and actual value between 0 and the LLOQ) in the analyses under PK Data Set Info will be performed for information only. The conventions to be applied for “No peak” under PK Data Set Info will be the same as the one use for BQL under PK Data Set. Descriptive statistics and PK concentration plots will be conducted on both data sets.

Descriptive statistics (n, 0<n<LLOQ, n with imputed 0, arithmetic mean, SD, geometric mean, geometric CV(%), median, min, and max) will be used to summarize the plasma concentrations for AZP-3601 by scheduled time point by study part and treatment (for Parts A and B)/cohort (for Part C). Plasma concentrations for AZP-3601 below the quantifiable limit (BQL) will be set to zero in the computation of descriptive statistics. Geometric means and geometric CV(%) will be presented as ‘NC’ (not calculable) if there is at least one BQL value imputed by zero.

Linear and semi-logarithmic plots of the arithmetic mean plasma concentration with SD by scheduled sampling time will be provided by study part and [redacted]/cohort (for Part C). These plots will show time in hours. [redacted] In Part[redacted] C, the MAD treatments will be presented in one plot per day. In addition, overlay plots for the MAD treatments will be presented, [redacted] showing Day 1, Day 14 and Day 28 in one plot for Part C (one plot per cohort). If more than half of the subjects for a given timepoint have BQL values, then no mean profiles will be provided.

Combined individual concentration-time profiles will be presented graphically on both a linear and a semi-logarithmic scale for each [redacted]/cohort (for Part C). MAD plots will show the profiles for each day.

Linear and semi-logarithmic plots of the individual plasma concentrations by actual sampling times will be provided by subject. These plots will show time in hours. MAD plots will show the complete profile. Individual plots will use the BQL handling procedure described below for “Pharmacokinetic Parameters”.

All individual subject plasma concentration data will be listed, including time deviations and comments.

15.2.2 Pharmacokinetic Parameters

PK parameters for AZP-3601 will be estimated using non-compartmental methods with WNL under PK population set with data handling of PK Data Set and PK Data Set Info (if meaningful by the data obtained). Parameters will first be derived with values under LLOQ set as “BQL” (i.e. using PK Data Set). The inclusion of the informative PK concentrations ("No peak” and actual value between 0 and the LLOQ) in the calculation of the parameters will be performed for information only (i.e. using PK Data Set Info). Descriptive statistics will be conducted on both data sets if meaningful by the data obtained.

The plasma PK parameters will be estimated from the concentration-time profiles. In estimating the PK parameters, BQL values at the beginning of the profile will be set to zero. BQL values that occur after the first quantifiable point will be considered missing. Values that are embedded between BQLs, or quantifiable values occurring after two or more BQLs, will be set to missing at the discretion of the pharmacokineticist. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time or dose time is missing, the scheduled time may be substituted in order to calculate the PK parameter.

The points to be included in the k_{el} range will be determined by the pharmacokineticist after inspection of the semi-log concentration-time profiles. At least 3 points will be required to be used. The C_{max} data point will not be included.

Parameters based on $\%AUC_{extra}$>20% or Adj R^2 ≤ 0.80 will be flagged but not excluded from statistical analysis.

Descriptive statistics (n, arithmetic mean, SD, geometric mean, geometric CV(%), median, min, and max) will be used to summarize the calculated PK parameters by study part and treatment (for Parts A and B) /cohort (for Part C). For t_{max}, only n, median, min and max will be presented.

15.2.2.1 Dose-Proportionality

[redacted]

16.0 Pharmacodynamic and other Analysis

16.1 Pharmacodynamic and other Variables

16.1.1 Serum PD Concentrations and Parameters

Part [redacted] C:

At the time points defined in the schedules of assessments, blood samples will be taken for the measurements of serum total calcium, serum albumin, albumin-corrected serum calcium, serum phosphate, serum creatinine (to calculate the fractional excretion (FECa) of calcium and phosphate), and endogenous serum PTH(1-84).

Serum PD variables include level/concentration of

- Serum total calcium
- Albumin-corrected serum calcium
  - Albumin-corrected serum calcium (mmol/L) = serum total calcium (mmol/L) + 0.020 (40 - serum albumin [g/L])
- Serum phosphate
- Endogenous serum PTH(1-84).

Furthermore, serum AUC_{0-24} for albumin-corrected calcium is a serum PD variable, which is defined as area under the serum concentration-time curve from time zero up to 24 hours for albumin-corrected calcium.

Part [redacted] only:

In addition to the PD variables listed above, at the time points defined in the schedules of assessments, blood samples will be taken for the measurements of serum 25-hydroxy vitamin D, serum 1.25-dihydroxy vitamin D, serum magnesium and serum bone turnover biomarkers.

Serum PD variables include level/concentration of

- Serum 1.25-dihydroxy vitamin D
- Serum Magnesium
- Serum 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)
  - Serum osteocalcin

Part C only:

In addition to the PD variables listed above, the following serum PD variables will be calculated:

- Serum calcium phosphate product
  - Serum calcium phospate product (mg2/dL2) = serum total calcium (mg/dL) * serum phosphate (mg/dL)
- Number of patients within the target range of albumin-corrected serum calcium
- Number of patients within the normal range of albumin-corrected serum calcium
- Number of patients within target range of albumin-corrected serum calcium who taking no vitamin D and taking <=500mg of oral calcium
- Number of patients within normal range of albumin-corrected serum calcium who taking no vitamin D and taking <=500mg of oral calcium,

where target range refers to 7.8 to 9.0 mg/dL and normal range refers to 8.3 to 10.6 mg/dL.

16.1.2 Urine PD Concentrations and Parameters

Part [redacted] C:

Urine will be collected during 24-hour collection intervals as defined in the schedules of assessments for the analysis of urine calcium, phosphate, creatinine (to calculate the FECa of calcium and phosphate and renal tubular maximum reabsorption of phosphate/glomerular filtration rate [TMP/GFR]) , [redacted] and magnesium.

The urine PD variables include

- 24-hour urine calcium (calcium excretion rate) = concentration of urine calcium * volume 24h sample
- 24-hour urine calcium adjusted by creatinine = concentration of urine calcium in the 24h urine/ concentration of urine creatinine in the 24h urine
- 24-hour urine calcium adjusted by body weight [1] = concentration of urine calcium * volume 24h sample / body weight
- 24-hour urine phosphate (phosphate excretion rate) = concentration of urine phosphate * volume 24h sample
- 24-hour urine cAMP (cAMP excretion rate) = concentration of urine cAMP * volume 24h sample

- Renal clearance of calcium = Urine Ae_{0-24} / Serum AUC_{0-24} for albumin-corrected calcium, where Ae_{0-24} is the total amount of calcium excreted unchanged into urine from time 0 to 24h
- Renal clearance of phosphate = Urine Ae_{0-24} / Serum AUC_{0-24} for phosphate, where Ae_{0-24} is the total amount of phosphate excreted unchanged into urine from time 0 to 24h
- FECa of calcium (%)[2] = 100 * urine calcium * serum creatinine / (serum calcium * urine creatinine)
- FECa of phosphate (%)[3] = 100 * urine phosphate * serum creatinine / (serum phosphate * urine creatinine)
- Tubular reabsorption of phosphate (TRP) = 1 - {(urine phosphate/serum phosphate) × (serum creatinine/urine creatinine)}
- Renal TMP/GFR = TRP × serum phosphate if TRP was ≤0.86; Renal TMP/GFR = 0.3 × TRP/[1 – (0.8*TRP)] × serum phosphate
- 24-hour urine magnesium (magnesium excretion rate) = concentration of urine magnesium * volume 24h sample (Only for Part C)

Note 1: for 24-hour urine calcium adjusted by body weight: "body weight" refers to the last measurement of body weight before the start of 24-hour interval of urine collection for each day.

Note 2: for FECa of calcium (%): "serum calcium" refers to the measurement at start of 24-hour interval of urine collection for each day.

Note 3: for FECa of phosphate (%): "serum phosphate" refers to the measurement at start of 24-hour interval of urine collection for each day.

16.1.3 Standard of Care

Part C only:

Standard of care will be evaluated at Baseline, at Day 14, at the end of the main treatment period (Day 28) and after 2 weeks during the extension period.

Variables for Standard of Care includes the following:

- Mean active vitamin D dose
- Mean calcium dose
- Number of patients
  - Taking neither vitamin D nor calcium
  - Taking no vitamin D and ⩽1000 mg/day of calcium
  - Taking no vitamin D and ⩽500 mg/day of calcium
  - Taking no vitamin D
  - Taking no calcium
  - Taking ⩽500 mg/day of calcium
  - Taking ⩽1000 mg/day of calcium

16.1.4 EQ-5D Questionnaire

Part C only:

EQ-5D will be used as a self-administered questionnaire measuring generic health status. The EQ-5D questionnaire has 2 components: health state description (using five-level scale) and evaluation (using a visual analogue scale).

Parameters from EQ-5D questionnaire

- Health state description
  - Mobility
  - Self-care
  - Usual activities
  - Pain/discomfort

  - Anxiety/depression
- Health state evaluation
  - Overall health status

16.1.5 SF-36 Questionnaire

Part C only:

Short form health survey 36 (SF-36) will be used as a self-administered questionnaire measuring generic health status.

The SF-36 consists of 8 scaled scores, which are based on the sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The lower the score, the more disability. The higher the score, the greater level of functioning i.e. a score of 0 is equivalent to worst functioning and a score of 100 is equivalent to best functioning. The health domain scales will be transformed to T Scores (refer to "User's Manual for the SF-36v2 Health Survey, 3rd Edition"). The 8 scaled scores will be calculated by PRO CoRe 2.0 Smart Measurement System. Missing data will be dealt with using Missing Data Estimation (MDE). Using MDE, the software applies a value to a scale item rendered missing if at least one of the items in that scale has valid data. A scale receives a "missing" score (".") only if all the items in that scale are missing.

- Parameters from short form health survey 36 (SF-36) questionnaire
  - Vitality
  - Physical functioning
  - Bodily pain
  - General health perceptions
  - Physical role functioning
  - Emotional role functioning
  - Social role functioning
  - Mental health

In addition to display of separate scales, component summaries will be shown:

  - Physical Component Summary (PCS), summarizing Physical functioning, Physical role functioning, Bodily pain, and General health perceptions

and

  - Mental Component Summary (MCS), summarizing Vitality, Social role functioning, Emotional role functioning, and Mental health

16.1.6 DXA Analysis

Part C only:

Bone mineral density (BMD) and Trabecurlar Bone Score will be assessed by DXA. DXA scans will be conducted using standardized procedures and settings. DXAs image will be read using independent central reading.

- Parameters from DXA Analysis
  - BMD (T Score and Z Score)
  - Trabecular Bone Score

16.2 Pharmacodynamic Evaluation

All individual concentration data for the PD assessments and all PD variables will be listed by subject.

16.2.1 Main PD Analysis

The main PD variables refer to the concentration of serum total calcium, albumin-corrected serum calcium and serum phosphate, as well as to the serum AUC_{0-24} for albumin-corrected calcium. The main PD variables will be summarized and listed in US standard units.

Descriptive statistics (n, arithmetic mean, SD, median, min, and max) summarizing the serum concentration for main PD variables (absolute observed value and change from baseline) will be presented by study part and [redacted]/cohort (for Part C) at each scheduled timepoint/day. Taking potential batch effect into consideration, the change from baseline will be calculated with corresponding baseline per batch if applicable; for different batches, all the assessments (absolute observed value and change from baseline (when possible)) will be presented with corresponding batch information separately. For the daily pre-dose timepoints, if a repeat/retest result is available, then the repeat/retest (Batch R) result will be used for the calculations.

[redacted]

Descriptive statistics (n, arithmetic mean, SD, median, min, and max) will also be used to summarize the serum AUC_{0-24} for albumin-corrected calcium. Change from baseline for that AUC will be listed and summarized, which is defined as area under the serum concentration-time curve from time zero up to 24 hours for change from baseline of albumin-corrected calcium.

In Part A, linear plots of the arithmetic mean serum concentrations of main PD variables (absolute observed value and change from baseline) with SD over all scheduled timepoints will be presented by treatment. In Part B, similar linear plots (absolute observed value and change from baseline) will also be provided for each summary tables of serum concentration as described above and presenting only the 24h profile versus time on Day 1, Day 7 and Day 14 (separately). In part C, similar linear plots will be provided by cohort for the main treatment period and for the extension phase separately.

16.2.2 Exploratory Analysis for other PDs and other Measurements

16.2.2.1 Serum

As to the other serum concentration of PD variables (endogenous serum PTH(1-84), serum 25-hydroxy vitamin D, serum 1.25-dihydroxy vitamin D, and serum bone turnover biomarkers), descriptive statistics (n, arithmetic mean, SD, median, min, and max) summarizing the panel data (absolute observed values and change from baseline) will be presented by study part, [redacted]) /cohort (for Part C) at each scheduled timepoint/day. For PTH(1-84), BQL values will be set to half of the LLOQ value.

As to the derived PD serum variables in Part C (serum calcium phosphate product, number of patients within the target range of albumin-corrected serum calcium, number of patients within the normal range of albumin-corrected serum calcium, number of patients within target range of albumin-corrected serum calcium who taking no vitamin D and taking <=500mg of oral calcium, number of patients within normal range of albumin-corrected serum calcium who taking no vitamin D and taking <=500mg of oral calcium) will be summarized descriptively by cohort and timepoint. The corresponding numbers and percentages of patients will be summarized at Baseline, Day 14, and Day 28.

16.2.2.2 Urine

As to the derived PD urine variables, descriptive statistics (n, arithmetic mean, SD, median, min, and max) will be used to summarize by study part, [redacted] /cohort (for Part C) and scheduled timepoint. For 24-hour urine calcium, 24-hour urine phosphate and 24-hour urine magnesium (for Part C only), descriptive statistics will also be provided for change from baseline.

In addition, linear plots will be provided for bone turnover biomarkers, in a way similarly as the linear plots mentioned above for main PD analysis.

16.2.2.3 Standard of Care

Summary and frequency table will be provided for each variable of standard of care by cohort at baseline, at day 14, at the end of main treatment period and every two weeks during extension.

Dosing amounts of supplements prescribed by investigators will be listed and used for the analysis of standard of care.

16.2.2.4 EQ-5D and SF-36

Descriptive statistics (n, arithmetic mean, SD, median, min, and max) will be used to summarize scores (absolute values and changes from baseline) for the parameters of these questionnaires by cohort at each scheduled day.

16.2.2.5 DXA Analysis

Descriptive statistics (n, arithmetic mean, SD, median, min, and max) will be used to summarize BMD and Trabecular Bone Score (absolute values and changes from baseline) by treatment dose level and at each scheduled day.

17.0 Safety Analyses

17.1 Safety Variables

The following safety variables will be summarized by study part (Part[redacted] C main, or C extension) if applicable:

- AEs
- Injection Site Reaction
- Clinical Laboratory Evaluations
  - Clinical Chemistry
  - Hematology
  - Coagulation
  - Urinalysis
- Vital Signs
  - Systolic Blood Pressure
  - Diastolic Blood Pressure
  - Pulse rate
  - Body temperature
- Electrocardiograms (ECG)
  - Heart Rate
  - PR-Interval
  - QRS-Duration
  - QT-Interval
  - QTc Friderica
- Part A only: Continuous cardiac monitoring (telemetry)
- Physical Examination
- Body Weight and BMI

- Antidrug antibodies (ADA) in plasma

17.1.1 Adverse Events

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to (the first) administration of the study drug or any event already present that worsens in either severity or frequency following exposure to the study drug.

An overall summary table will be provided by treatment and overall for each study part with the number of subjects and events reporting, AEs, TEAEs, treatment-emergent SAEs, treatment-emergent AEs of special interest (AESIs), and TEAEs leading study drug discontinuation.

Based on the pharmacology of AZP-3601 as well as other PTH analogs, and the pathophysiology of HP, AESIs are as follows:

- Hypocalcemia (including the following symptoms: agitation, anxiety, hypoestesia, paresthesia, muscle cramping, muscle fatigue, musculoskeletal pain, musculoskeletal stiffness, myalgia, tetany, seizure, tremor, brain fog).
- Hypercalcemia (including the following symptoms: thirst, frequent urination, abdominal pain, nausea, vomiting, fatigue).
- Hypercalciuria.
- Orthostatic hypotension and vasodilatory symptoms (including postural/orthostatic dizziness, syncope, tachycardia/palpitations).

A summary table with the number of subjects reporting TEAEs and the number of events, categorized by system organ class (SOC) and preferred term (PT) coded according to the MedDRA, will be presented by [redacted] /cohort (for Part C) and overall for each study part. Subjects will only be counted once within each system organ class or preferred term.

A summary table with the number of subjects reporting TEAEs, categorized by SOC, PT and relationship to study drug (Related or Not Related), will be provided by [redacted] /cohort (for Part C) and overall for each study part. A treatment-related TEAE is defined as any TEAE that is assessed by the investigator as definitely, likely, possibly or unlikely related to study treatment. TEAE that is assessed as Not Related will be defined as not treatment-related. Subjects with multiple events within a particular body system or preferred term will be counted under the category of their most drug-related event within that body system or preferred term.

A summary table with the number of subjects reporting TEAEs, categorized by SOC, PT and severity as recorded on eCRF (Mild, Moderate, Severe, Life-threatening or Death), will also be provided by [redacted] /cohort (for Part C) and overall for each study part. Subjects with multiple events within a particular body system or preferred term will be counted under the category of their most severe event within that body system or preferred term.

A summary table with the number of subjects reporting treatment-emergent AESIs and the number of events, categorized by SOC and PT coded according to the MedDRA, will be presented by treatment (for Parts A and B)/cohort (for Part C) and overall per for each study part. Subjects will only be counted once within each body system or preferred term.

The following missing data will be imputed as defined (for calculations only / will not be presented):

- Missing AE severity or relationship will be assumed to be severe or related, respectively
- Missing AE start times for the determination of treatment emergence will be assumed to occur after treatment unless partial date documents the AE as happening prior to treatment
- Missing AE start date will be assumed to be after treatment for the determination of TEAE unless partial or complete end date documents the AE as happening prior to treatment

All AEs (including non-treatment-emergent events) recorded on the eCRF will be listed, with a flag to indicate whether the AEs are AESIs.

A separate listing of TEAEs leading to study drug discontinuation will be provided.

17.1.2 Deaths and Serious Adverse Events

A listing of deaths and other serious adverse events (SAE) will be provided by subject.

17.1.3 Injection Site Reactions

Injection site reactions as collected on the CRF will be listed per subject.

A summary table with the number and percentage of subjects reporting injection site reactions, categorized by severity evaluation, will be presented by [redacted] /cohort (for Part C) and overall at each scheduled assessment timepoint for each study part.

17.1.4 Laboratory Data

Clinical laboratory data will be presented using standard units from the SDTM Controlled Terminology.

Descriptive statistics summarizing continuous laboratory results of clinical chemistry, hematology and coagulation (absolute observed and derived changes from baseline) for each study part by [redacted] /cohort (for Part C) and scheduled time will be presented.

Frequency table summarizing categorical laboratory results of urinalysis for each study part by [redacted] /cohort (for Part C) and scheduled time will be presented, if appropriate.

All laboratory data will be listed by subject.

A separate listing of clinically significant abnormal values will also be provided.

17.1.5 Vital Signs

Descriptive statistics summary of vital signs and derived changes from baseline will be provided for each study part by [redacted] /cohort (for Part C) and scheduled time point.

All vital signs data (including changes from baseline) will be listed by subject.

17.1.6 Body Weights and BMI

Descriptive statistics summary of body weights and BMI and derived changes from baseline will be provided for each study part by [redacted] /cohort (for Part C) and scheduled time point.

All body weights and BMI data (including changes from baseline) will be listed by subject.

17.1.7 Electrocardiograms

A descriptive statistics summary of continuous 12-lead ECG parameters and derived changes from baseline will be provided for each study part by [redacted] /cohort (for Part C) and scheduled time.

[redacted]

All ECG parameters (including changes from baseline) and the corresponding abnormalities and physician's conclusions will be listed by subject.

[redacted]

17.1.9 Physical Examination

The physical examination findings (abnormalities) at screening and changes /new findings after screening will be listed.

17.1.10 ADA in Plasma

The presence of ADA in plasma will be listed if applicable.

18.0 References

Clinical Study Protocol: 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. Global Version 5.0, 12May2021.

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