The effect of FP-025, a MMP-12 inhibitor, on allergen-induced airway responses, airway inflammation and aspects of airway remodeling in subjects with mild eosinophilic house dust mite (HDM)-allergic asthma

(HDM)-allergic asthma

Protocol Number: FP02C-18-001

NCT: 03858686

SAFETY STATISTICAL ANALYSIS PLAN

Protocol Title:	The effect of FP-025, an MMP-12 inhibitor, on allergen-induced airway responses, airway inflammation and aspects of airway remodeling in subjects with mild eosinophilic house dust mite (HDM)-allergic asthma
Sponsor's Protocol Number:	FP02C-18-001
QPS Study Number:	160509
Sponsor Name and Address:	Foresee Pharmaceuticals Co., Ltd 9F-2, No. 19-3, Sanchong Rd., Nangang District Taipei 115, Taiwan
Date and Version of SAP:	30 March 2023, Final version 1
Prepared by:	[redacted]

QPS AUTHORS' SIGNATURE PAGE

REVIEWED BY:

[redacted]

30 March 2023 | 21:04 CST

Date

[redacted]

30 March 2023 | 21:48 CST

Date

SPONSOR'S SIGNATURE PAGE

APPROVED BY:

[redacted]

30 March 2023 | 07:45 PDT

Date

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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADaM	Analysis Data Model
ADSL	Subject-Level Analysis Dataset
AE	Adverse Event
AMC	Academic Medical Centre
AUC	Area Under the plasma concentration Curve
BA	Bioavailability
BMI	Body Mass Index
BP	Blood Pressure
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
DBL	Database lock
EAR	Early Asthmatic Response
EBC	Exhaled Breath Condensate
ECG	Electrocardiogram
eCRF	electronic CRF
EOS	End-of-study
FeNO	Fractional exhaled Nitric Oxide
FSH	Follicle Stimulating Hormone
HDM	House Dust Mite
HR	Heart rate
IOS	Impulse-oscillometry
LAR	Late asthmatic response
LOQ	Limit of Quantitation
MedDRA	Medical Dictionary for Regulatory Activity
MH	Medical history
MMP	Metalloproteinase
NAB	Nasal Brush
NAL	Nasal Lavage
NCS	Not clinically significant
PBMC	Peripheral Blood Mononuclear Cell
PEF	Peak Expiratory Flow
PD	Pharmacodynamic(s)
PI	Principal Investigator(s)
PK	Pharmacokinetic(s)
PKAP	PK Analysis Plan
PT	Preferred term
SAE	Serious AE
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SI	Sputum Induction
SOC	System Organ Classification
SpO2	Peripheral Oxygen Saturation
TEAE	Treatment-emergent AE

VAS	Visual Analogue Scale
VS	Vital signs
WHO	World Health Organization

3 INTRODUCTION

This safety statistical analysis plan (SAP) is based on the final version of protocol FP02C-18-001 amendment 3, dated 06 September 2021. The SAP provides details of data handling procedures and statistical analysis methods for safety evaluations. It also outlines statistical programming specifications for tables and listings, and other details on the analyses not provided in the study protocol.

Pharmacokinetic (PK) and pharmacodynamic (PD) profiles and relationship between PK and PD will be defined in the Pharmacokinetic and Pharmacodynamic Analysis Plan (PKPDAP).

4 DOCUMENTS USED

Study Protocol
The effect of FP-025, an Metalloproteinase (MMP)-12 inhibitor, on allergen-induced airway responses, airway inflammation and aspects of airway remodeling in subjects with mild eosinophilic house dust mite (HDM)-allergic asthma, FP02C-18-001, amendment 3, and Date of Release: 06 September 2021

Source/Case Report Form (CRF)
CRF, Version 2, Date of Release: 15 June 2021

4.1 Study Objectives

Primary Objective

- To determine the effect of FP-025 versus placebo on the allergen (HDM)-induced late asthmatic response expressed as FEV_1 $AUC_{3\text{-}8h}$ in subjects with clinically stable, mild allergic asthma and blood eosinophilia.

Secondary Objectives

- To determine the PD of FP-025 versus placebo on additional markers of airway physiology, including (additional measures of) the early and late response, airway hyperresponsiveness and small airways function; inflammatory markers (including blood eosinophils and FeNO) following inhaled HDM-challenge in subjects with clinically stable, mild allergic asthma and blood eosinophilia.
- To determine the treatment effect (i.e. Day 1 versus Day 10) of multiple oral doses of FP-025 versus placebo on baseline parameters (such as (but not limited to) blood eosinophils, FeNO and $PC20FEV_1$(Meth) or $PC20FEV_1$(Hist)).
- To determine the safety and tolerability of multiple oral doses of FP-025 versus placebo in subjects with clinically stable, mild allergic asthma and baseline blood eosinophilia.
- To assess the PK of multiple oral doses of FP-025 following inhaled HDM-challenge in subjects with clinically stable, mild allergic asthma and baseline blood eosinophilia.

Exploratory Objectives (including but not limited to):

- To explore the effect of FP-025 versus placebo on:
  - Cellular and soluble inflammatory biomarkers (including activation and leakage markers) in nasal lavage (NAL) and sputum;

- Nasal gene and microRNA expression in nasal brush (NAB);
- (Inflammatory) biomarkers in exhaled breath condensate (EBC), blood (eosinophil activation markers and potentially others as well) and urine (lipid mediators);
- Functional in vitro responses of peripheral blood mononuclear cells (PBMC);
- Expression and activity of MMP-12, other MMP's and markers of tissue remodeling in blood, sputum and potentially in NAL.

Deviations from the analyses in the exploratory objectives and additional objectives/analyses may be considered depending on analysis/outcomes of primary and secondary objectives and/or exploratory parameters (e.g. the duration of treatment effect on lung function measurements ± biomarkers). These changes are decided upon jointly by PI's and Foresee.

4.2 Data Sources

All analyses defined in this SAP will be carried out using the data from the electronic CRF (eCRF) and external data including central lab data, biomarkers, bioavailability (BA) data, and checked/monitored/QCed excel spread sheets of lung function data if applicable.

Clinical dataset extracted from OpenClinica interface enterprise edit version 3.11 and other external data will be converted to Study Data Tabulation Model (SDTM) datasets and Analysis Data Model (ADaM) datasets. Data listings and summary tables will be generated based on SDTM datasets and ADaM datasets.

5 OVERALL STUDY DESIGN AND PLAN

5.1 Study Design

This is a randomized, placebo-controlled, double-blind, 2-way cross-over, 2-centre study in male and female subjects with stable, mild HDM-allergic asthma and baseline blood eosinophilia.

Prior to the study, there will be a Screening period consisting of 3 clinic visits (within approximately 7 weeks) to test subject eligibility.

On Screening Day 1, the following procedures will take place: signing of the informed consent, a check of the inclusion/exclusion criteria, medical history and demographics, physical examination, measurements of vital signs, height and weight, calculation of body mass index (BMI), blood sampling for blood eosinophils and clinical safety laboratory assessments, electrocardiogram (ECG), allergy testing and screening for drug and alcohol use, smoking (i.e. cotinine), pregnancy and HIV, Hepatitis B and Hepatitis C (i.e. serology). At the discretion of the Principal Investigators (PI) or sub-investigators, some Screening Day 1 assessments (e.g. safety lab/pregnancy test/drug screen/cotinine screen/physical examination) may be moved to and/or repeated on Screening Day 2 and/or Screening Day 3.

Within approximately 40 days after Screening Day 1, potentially eligible subjects will start with more specific screening procedures (on 2 separate days (Screening Day 2 and Screening Day 3), preferably within 5 days but maximally within 8 days). Subjects will be called by a physician or research staff within approximately 1 week prior to Screening Day 2 to check their asthma

stability/medication intake/general health status. On Screening Day 2, spirometry with subsequent methacholine/histamine challenge (for calculation of the $PC20FEV_1$(Meth) or $PC20FEV_1$(Hist)) will be performed, followed by sputum induction (SI). If logistics allow, impulse-oscillometry (IOS) will be added to spirometric measurements. On Screening Day 3, there will be an inhaled HDM challenge with airway response measurements (including IOS and spirometry) during and up to approximately 8 hours post-allergen (if during screening, at 8 hours post-allergen the FEV_1 drops between 10-15% from post-diluent baseline, additional FEV_1 measurements may be conducted until 9 hours post-allergen (8.5 and 9 hours). On completion of all response measurements following both inhalational challenges on Screening Day 2 and 3, subjects will receive rescue bronchodilator medication and lung function will be measured. Upon leaving the clinic, all subjects will be provided with rescue medication (short acting beta2-agonist) to be used on an 'as needed basis' throughout the study. In addition, after each inhalational challenge, subjects will receive emergency instructions, and will be provided rescue medication (Ventolin). Within approximately 48 hours after Screening Day 3, subjects will be called by a physician to check their asthma status/rescue medication use and general health.

Following a washout period of at least 3 weeks and up to approximately 7 weeks, eligible subjects will be enrolled into the study and randomized on Day 1 if their asthma is within continuation criteria of screening (as assessed by history, (rescue) medication use, baseline FEV_1 and $PC20FEV_1$(Meth) or $PC20FEV_1$(Hist)). The study will consist of two identical study periods of 12 treatment days each, separated by a washout period of at least 3 weeks (and up to approximately 7 weeks). Approximately 36 eligible subjects will be enrolled, to yield 32 evaluable subjects who will be treated with both FP-025 (400 mg BID) or placebo in a cross-over design from the evening of Day 1 till the morning of Day 12 (22 doses per study period in total). Based on a double-blind randomized schedule, 16 subjects will receive placebo in Period 1 and FP-025 in Period 2 and 16 subjects will receive FP-025 in Period 1 and placebo in Period 2. Both study periods will follow the same schedule of procedures.

Subjects will be called by a physician or research staff within approximately 1 week prior to Day -1 of each study period to check their asthma stability/ medication intake/ general health status. On Day -1, the checks performed on Screening Day 1 (i.e. medical history (includes asthma medication use, Adverse Events and asthma stability check)), physical examination, vital signs, weight, ECG, blood collection for clinical safety laboratory assessments and drug, alcohol, cotinine and pregnancy testing) will be repeated to reconfirm eligibility. Subjects stay overnight in the unit at the discretion of the (co)PI.

On Day 1, after a short checklist, the following tests will be performed for baseline purposes, i.e. blood and urine sampling (both for routine safety and biomarkers), FeNO, IOS (if logistics allow), spirometry, EBC, NAL, NAB, methacholine/histamine challenge (with calculation of $PC20FEV_1$(Meth) or $PC20FEV_1$(Hist) for stability/eligibility check) and SI.

On Day 1 of Period 1, subjects should still have stable asthma (based on continuation criteria as applicable in the allergen challenge: i.e. history/medication use/spirometry and $PC20FEV_1$(Meth) or $PC20FEV_1$(Hist)) in order to be randomized by a blinded pharmacist and start with the study drug administration. Should a subject not comply to the stability criteria, (s)he may be rescheduled at the discretion of the (co)PI, depending on the underlying cause.

Starting on Day 1 with an evening dose, FP-025 or placebo will be given over 12 days (BID from Day 2 up to and including Day 11, final morning dose on Day 12) to ensure stable FP-025 levels during Days 10-12 (outcome measure days).

To aid compliance, during Day 2-9, subjects will either receive study medication onsite the clinic (observed dosing) or take their study medication at home or combinations of these. In the event study medication will be taken at home (between 6-10 am/pm), the subject will be contacted twice a day on dosing days to receive confirmation of study medication intake. In addition, from Screening Day 3 onwards and during study, subjects will be keeping track of their rescue medication use and AEs in a diary.

On Day 5 (±1 day) subjects will return to the clinic for safety monitoring, study requirements compliances and observed study medication intake during morning or evening doses.

In the evening of Day 9, depending on their place of residence and asthma status, subjects will come onsite to the clinic to check and ensure asthma stability ± undergo additional checks (safety lab/cotinine/alcohol/drug screen; as indicated in flowchart) before subsequent tests on Days 10-12.

On Day 10 (i.e. approximately 24 hours pre-allergen), approximately 30-60 minutes after first daily dosing, subjects undergo the same procedures as on Day 1 (i.e. safety/stability check, blood and urine collection (biomarkers), FeNO, EBC, NAL, NAB, IOS (if logistics allow), spirometry, methacholine or histamine challenge and SI. Subjects stay overnight in the unit. On Day 11, approx. 30-60 minutes after the morning dose, an inhaled allergen (HDM) challenge will be performed with airway response measurements (IOS and spirometry). During this study day, repeated PK sampling and blood biomarker sampling will be performed. EBC, NAL and NAB will be performed at approximately 6.5 hours post allergen challenge. Subjects stay overnight in the unit. On Day 12 (approximately 24 hours post-allergen), 30-60 minutes after the last study medication (i.e. morning) dose, the same procedures as on Day 10 will be repeated. Furthermore, clinical safety laboratory assessments will be performed. Clinically stable subjects will receive written instructions, including emergency numbers, and rescue medication prior to leaving the clinic. Within approximately 72 hours after Day 12 of each study period, subjects will be called by a physician to check their asthma/medication intake/AEs and general health. If deemed necessary by the (co)PI, there may be another check on the subjects before and/or after each study period and in any case following drop-out (either by phone or if needed and in case of drop-out, onsite the clinic).

Fourteen (14) days (± 2 days) after final administration of FP-025 or placebo on Day 12 of Period 2, a follow-up visit will be scheduled. This visit will not only serve as a follow-up visit (e.g. checking weight and AEs, performing physical examination, ECG and pregnancy test, checking vital signs and collecting blood for clinical safety laboratory assessments), the ‘duration of efficacy’ will also be explored by performing the same procedures as performed on Day 1 and Day 10 (i.e. blood and urine samplings (safety/biomarkers), FeNO, EBC, NAL, NAB, IOS (if logistics allow), spirometry, methacholine or histamine challenge and SI).

The details regarding the timing of specific procedures, see Table 5.1.

5.2 Endpoints

Primary Endpoint

The primary endpoint of this study is the effect of study treatments on FEV_1 AUC_{3-8h} during the Late asthmatic response (LAR) (FP-025 versus placebo).

Secondary Endpoints

- PD endpoints include the effect of study treatments (comparison of FP-025 vs. Placebo) on allergen (HDM)-induced (changes in):
  - LAR expressed as max% fall in FEV_1 from post-diluent baseline (3-8 h post-allergen challenge);
  - Early asthmatic response (EAR) expressed as FEV_1 AUC_{0-3h};
  - EAR expressed as max% fall in FEV_1 from post-diluent baseline (0-3 h post-allergen challenge);
  - Joint HDM-induced airway response expressed as AUC_{0-8h};
  - Airway hyperresponsiveness expressed as $PC20FEV_1$(Meth) or $PC20FEV_1$(Hist) (Day 10-Day 12); (i.e., the difference in allergen-induced airway hyperresponsiveness between treatments – expressed as the difference in the delta's PC20FEV1(Meth) or PC20FEV1(Hist))
  - Small airway parameters following HDM-challenge (i.e. R5, R20, R5-R20, AX, X5, Fres) – analysed as AUCs 0-8h post-allergen);
  - FeNO (day 12 vs day 10: comparison between treatments on allergen-induced changes in FeNO levels);
  - Blood eosinophils.
- Potential treatment effect (FP-025 versus placebo) on baseline parameters (i.e. Day 1 versus Day 10), including:
  - Blood eosinophils;
  - $PC20FEV_1$(Meth) or $PC20FEV_1$(Hist);
  - FeNO
- Safety parameters include physical examination, clinical signs/symptoms reporting (Medical Dictionary for Regulatory Activity MedDRA)), (Serious) adverse events ((S)AEs), vital signs, lung function measurements, overall asthma symptoms, ECG and clinical safety laboratory outcomes (blood/urine).
- PK parameters of FP-025 in blood (plasma) include C_{max}, t_{max}, and AUC_{0-tau}.
- Any relevant correlations between the abovementioned parameters (e.g. LAR AUC_{3-8h} vs PK parameters; as well as correlations between physiological and biomarker analyses).

This SAP will only answer the safety endpoints in the secondary endpoints. PK and PD analyses are not in the scope of this SAP.

Exploratory Endpoints

Exploratory PD parameters of FP-025 (Day 10 versus Day 12 = treatment effect on HDM-induced (airway) responses; and Day 1 versus Day 10 = treatment effect on baseline parameters) include:

- Cellular and soluble markers of inflammation in NAL and sputum, i.e.: eosinophil and lymphocyte counts, total cell counts, levels of ECP, MPO, IL-1b, FGF, VEGF and IL-5 and

relative coefficient of excretion (RCE: ratio A2M in sputum/NAL relative to that in serum divided by the ratio of albumin sputum/NAL relative to that in serum);
- Genome-wide gene and microRNA expression and DNA methylation in NAB samples;
- Biomarkers of oxidative stress and cellular activation in EBC;
- Cellular (eosinophil activation) and soluble inflammatory mediators (IL-5) in blood;
- Lipid mediators in urine (to be determined; leukotrienes);
- PBMC counts and functional parameters (cytokine release; Elispot assay);
- Expression and activity of MMP-12, other MMP's and markers of tissue remodeling in blood, NAL and sputum;
- Potentially longer lasting treatment effects 14 days following Period 2 (FP-025 versus placebo) (spirometry (baseline FEV_1), $PC20FEV_1$(Meth) or $PC20FEV_1$(Hist) and airway and systemic biomarkers (i.e. blood/urine/exhaled air (FeNO, EBC), NAL/NAB; sputum).

5.3 Study Medication

Each subject will receive 22 doses of 400 mg FP-025 (8x 50 mg capsules, BID) or 22 doses of matching placebo (8 capsules, BID) during two study periods with a washout period of at least 3 weeks and up to approximately 7 weeks.

5.4 Randomization and Blinding

Subjects will be randomly allocated to start with either placebo or FP-025 in Period 1. The randomization code is stored securely. It is accessible only to authorized persons who are not involved in the conduct and analysis of the study, until time of unblinding.

5.5 Sample Size

Approximately 100 male and female HDM-allergic asthmatics (between 18 and 55 years of age at Screening, inclusive) will be screened to yield approximately 36 eligible subjects to be enrolled, to yield 32 evaluable subjects.

The sample sizes for this study are based on previous allergen challenge studies and previous local experiences including several outcomes (airway physiology and several (diluted) biomarkers), taking into account additional variability due to a 2 centre setup.

The data of screening failure subjects will not be presented in the tables and listings.

5.6 Study Flow Chart/Schedule of Events (SOE)

The study will consist of a Screening period (within 7 weeks), two treatment periods (with at least 3 weeks washout period), and an End-of-Study (EOS)/Follow-up evaluations (Day 14 ± 2 days).

The complete schedule of prescheduled visits and all procedures is presented in Table 5.1.

Table 5.1: Visit and Assessment Schedule

Study Period	Screening within 6 weeks (followed by a washout period of 3-7 weeks)[a]			Treatment Period 1 and 2 (consecutive days) (washout period of 3-approximately 7 weeks between periods)										EOS/ Follow-up
Study Day	**S1**	**S2**	**S3**	**-1**	**1[b]**	**2-4**	**5 (± 1 day)**	**6-8**	**9**	**10[c]**	**11**	**12[c]**	**<7 days after dosing on Day 12**	**14 ± 2 days after last dosing**
Informed consent	X													
Height	X													
Weight	X			X										X
BMI	X													
In-/exclusion criteria[d]	X	X		X										
Reconfirmation of Eligibility[e]		X	X	X										
Demographics	X													
Medical history	X			X										X
Physical examination	X			X										X
Allergy testing[f]	X													
Vital signs[g]	X			X					X		X			X
12-lead ECG[g]	X			X					X					X
Clinical safety laboratory tests in blood and urine (including blood eosinophil count, coagulation and hematology)[g]	X			X					X			X		X
Virus serology (i.e. hepatitis B and C, HIV)	X													

Study Period	Screening within 6 weeks (followed by a washout period of 3-7 weeks)[a]			Treatment Period 1 and 2 (consecutive days) (washout period of 3-approximately 7 weeks between periods)										EOS/ Follow-up
Study Day	**S1**	**S2**	**S3**	**-1**	**1[b]**	**2-4**	**5 (± 1 day)**	**6-8**	**9**	**10[c]**	**11**	**12[c]**	**<7 days after dosing on Day 12**	**14 ± 2 days after last dosing**
Urine drug screen [g]	X			X						X				
Alcohol breath test [g]	X			X						X				
Cotinine screen [g]	X			X						X				
Pregnancy test[h]	X			X										X
Inhaled allergen (HDM) challenge			X								X			
FeNO in exhaled air					X					X		X		X
EBC					X					X	X	X		X
Nasal lavage and nasal brush[i]					X					X	X	X		X
IOS[j]		X	X		X					X	X	X		X
Spirometry[k]		X	X		X					X	X	X		X
Methacholine challenge		X			X					X		X		X
(Optional) overall asthma symptoms[l]					X					X	X	X		
Randomization[m]					X									
Sputum induction		X			X					X		X		X
Blood collection for inflammation markers and biomarkers[n]					X					X	X	X		X
Urine collection for biomarkers (i.e. lipid mediators)					X					X	(X)	X		X

Study Period	Screening within 6 weeks (followed by a washout period of 3-7 weeks)[a]			Treatment Period 1 and 2 (consecutive days) (washout period of 3-approximately 7 weeks between periods)										EOS/ Follow-up
Study Day	**S1**	**S2**	**S3**	**-1**	**1[b]**	**2-4**	**5 (± 1 day)**	**6-8**	**9**	**10[c]**	**11**	**12[c]**	**<7 days after dosing on Day 12**	**14 ± 2 days after last dosing**
Oral dosing of FP-025 or placebo (twice daily from Day 2 onwards)[o]					X	X	X	X	X	X	X	X		
PK blood sampling[p]											X			X
Ambulant visits	X	(X)	(X)			(X)	X	(X)	(X)					X
Residence in clinic[q]		(X)	(X)	X	X				(X)	X	X	X		
Dispense diary			X											
Subject instructions and/or diary review[r]			X				X				X			
Check treatment compliance (e.g. observed dosing, diary and phone calls)					X	X	X	X	X	X	X	X		
Check health status		(X)	(X)	X	X				(X)	X	X	X		
Phone call[s]		X	X	X		X		X	(X)				X	
Adverse events	<---------- Continuously ---------- >													
Concomitant medications (including rescue medication)[t]	<---------- Continuously ---------- >													

a. At the discretion of the PI or sub-investigator, Screening Day S1 some assessments (e.g. safety lab//pregnancy test/drug screen/cotinine screen/physical examination) can be moved to and/or repeated on Screening Day S2 and/or Screening Day S3. Screening Day S2 should start within approximately 40 days after Screening Day S1. Screening Day S3 preferably should start within 5 days after Day S2 but maximally within 8 days after Day S2.

b. FeNO, EBC, NAL, NAB, spirometry, methacholine/histamine challenge and SI to be performed in the morning (pre-dose). On Day 1, spirometry will

be performed immediately after FeNO (since eligibility criterion).

c. All procedures, except ECG on Day 10, are to be started 30-60 minutes following first daily dose. On Day 10 procedures should be performed 24±1 hour before starting inhaled allergen challenge (Day 11) and on Day 12 procedures should be performed 24±1 hour after (the start of) inhaled allergen challenge.
d. Only on Screening Day S1, Screening Day S2 and Day-1 of Treatment Period 1.
e. By Medical history/Medication use/FEV_1 and $PC20FEV_1$(Meth) or $PC20FEV_1$(Hist).
f. Not needed if allergic status can be based on historically demonstrated allergy, either by SPT or serology; otherwise by serum allergen specific IgE measurement (or SPT) at Screening.
g. Assessment on Day 9 may also be performed prior to all other tests on Day 10.
h. Female subjects only: serum pregnancy test at Screening, urine pregnancy test at Day -1 and EOS.
i. Day 1: pre-dose, Day 10: 24±1 hour before starting inhaled allergen challenge, Day 11: approx. 6.5 hours after inhaled allergen challenge, Day 12: 24±1 hour after the start of inhaled allergen challenge.

6 DESCRIPTION OF INCLUDED SUBJECTS

6.1 Analysis Sets

6.1.1 All-treated set

This analysis set includes all randomized subjects who received study drug (at least one dose). This population will be used for the summary of subject disposition, demographics, and treatment effect.

6.1.2 Safety set

This analysis set includes subjects from the all-treated set who had at least one safety assessment post-baseline. The safety set will be employed in the analysis of tolerability and safety variables.

6.1.3 Per-protocol set

This analysis set comprises all subjects included in the all-treated set who did not violate the protocol in a way that might affect the evaluation of the effect of the study drug on the primary endpoint, i.e., without major protocol violations or deviations. The per-protocol set will be employed in the analysis of PK variables.

6.2 Status of the Subjects

The status of the subjects will be presented using an ADaM status dataset, the Subject-Level Analysis Dataset (ADSL), which will be created and used throughout the summary tables.

6.3 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol. All identified protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment will be collected during the conduct of the study and listed.

The Protocol Deviation list is a list that presents the deviations by subject, description of actual deviation, and by type/category. The Protocol Deviation list will serve as input for the selection of subjects for inclusion in the per-protocol set. The generation of the Protocol Deviation list is created by the Data Manager, but may involve collaboration with the Biostatistician and/or SAS programmer, and is preferably based upon a predefined set of protocol deviations that is as inclusive as possible.

7 REPORT SPECIFICATIONS AND STATISTICAL ANALYSES

7.1 General Considerations

For safety, tolerability, and treatment effect analyses of some of PD parameters, the descriptive statistics presented will include frequency counts (n) and percentage for qualitative variables. Quantitative variables will be summarized using n, arithmetic mean, standard deviation (SD), median, minimum, maximum, and number of missing observations.

Appropriate rounding will be performed for the summary tables: arithmetic mean and median will be presented with one more decimal than the original data; SD will be presented with two more decimals than the original data; minimum and maximum values will be presented with the same precision as the original data. Percentages will be presented with 2 decimals and no decimals will be presented for integer values, e.g., zero will be presented as 0%.

Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics but will be included in subject listings only.

Pre-treatment baseline is defined as the last non-missing value measured prior to (the first) study drug intake for vital signs, laboratory parameters, and safety lung function, unless otherwise specified. For ECG, the average of the 3 recordings made with a 1-minute interval between recordings at Day -1 of each period will be taken as baseline. For summary of change from baseline, only the subjects who have both baseline and post-baseline values will be included.

In general, data will be presented for each treatment or sequence group. For disposition, demographics, and safety assessments including adverse events, laboratory outcomes, ECG, PE, VS and Lung function measurement, data for all study subjects combined as “All Subjects” will be also presented.

For the summary of laboratory results reported as above limit of quantification (>LOQ), the numeric value will be the LOQ value plus one unit of the minimum digit of the given parameter; for any laboratory results reported as below LOQ (<LOQ), the numeric value used for summary will be set to half of the LOQ value. For example, if the laboratory result is ‘>2’, the numeric value to be summarized will be 2 plus 1 which is 3; if the result is ‘<0.5’, the numeric value to be summarized will be set to half of 0.5 which is 0.25.

No statistical inference will be performed for safety evaluation.

Note: some minor modifications may be necessary to the planned design of tables and listings to accommodate data collected during the actual study conduct. This is not considered a deviation from the preplanned statistical analysis.

7.2 Incomplete and Missing Data

All analyses will be performed on data available at the time point considered. In summary tables, the number of subjects with missing data will be presented unless otherwise specified. In

calculation of percentages, subjects with missing data if not included in an analysis will not be considered in numerator or denominator unless otherwise specified.

7.3 Demographic and Baseline Characteristics

Descriptive tabulations of the screening data for demographics will be made. Demographic data (including height, weight, body mass index (BMI) and blood eosinophils at Screening Day 1 and $PC20FEV_1$(Meth) or $PC20FEV_1$(Hist) and FEV_1 in % predicted value at Screening Day 2 will be presented for the all-treated set by sequence group and all study subjects combined. Appropriate descriptive statistics for age, sex, female reproductive status, race, ethnicity, smoking history, height, weight, BMI, blood eosinophils, $PC20FEV_1$(Meth) or $PC20FEV_1$(Hist), FEV_1 in % predicted value and previous medication (yes or no) will be given. Additionally, demographic data will be listed.

Age and BMI will be taken from the eCRF/database, not calculated by SAS.

Other baseline data, such as medical history, subject who did not meet in-/exclusion criteria, allergy testing, and clinical laboratory tests of follicle stimulating hormone (FSH) and virus serology will only be listed.

Medical history (MH) data will be coded with the latest version of the MedDRA coding system before DBL: this is version 25.1 or higher. The SAS programmer or Data Manager of the study will add the coding (using the MedDRA system and SAS) to the MH descriptions extracted from the database.

Prior medications are defined as any medication discontinued prior to the first dose of study drug. Concomitant medications are defined as any medication taken during the course of the study or started prior to the first dose of study drug and continued during the treatment. A subject listing of all previous and concomitant medications will be provided as two separate listings. Prior and concomitant medication will be coded with the latest version of the WHODrug Global B3-format September, 2022 or higher.

Based on the status dataset (see Section 6.2), a summary of randomization, completed study, the primary reason for discontinued the study, and in-/exclusion of analysis sets by sequence group, as well as overall, will be given (‘subject disposition’).

7.4 Subjects Disposition

The subject disposition will be given in a summary table by sequence group, as well as overall:

- the number of subjects randomized
- the number of subjects completed the study
- Of those who discontinued the study, the primary reasons for discontinuation
- the number of subjects in the all-treated set
- the number of subjects in the safety set
- the number of subjects in the per-protocol set

In addition, these data will be listed in a Subject Disposition listing. Reasons for discontinuation will be listed in the Study Disposition (Completion Status) listing, together with the relevant dates, and the reason for exclusion from analysis sets will be listed in Subjects Excluded from the Analysis listing.

7.5 Interim Analysis

After at least 11 subjects have successfully completed both treatment periods (with fully analyzable data sets of airway responses and sputum cytospins), an interim analysis will be conducted in order to compute the conditional power of a significant difference between FP-025 and placebo treatment on the LAR as well as on the sputum eosinophil counts (reflecting target engagement), at the planned end of the trial in the presence of sufficiently high PK levels and at the original expectation of the effect of FP-025 on the LAR. If the conditional power is less than 25%, the trial may be stopped for futility. However, such a decision will depend on the size of the FP-025 treatment-effect on secondary and exploratory outcomes.

In addition, the size of a potential carry-over effect of active treatment in the first treatment period into effects of treatment in the second treatment period will be investigated.

If the size of the carry-over is significantly larger than zero, the statistical analysis for the remaining subjects will be amended.

No adjustment of the sample size is made because with the intended sample size of 32 evaluable subjects, the power of the original effect is over 95% and this remains the case with the addition of the interim analysis.

In the absence of any clinically relevant AEs, recruitment and study conduct will continue during (preparation of) the interim analysis.

The interim analysis will be conducted by an independent statistician of Amsterdam UMC, AMC, Prof. A.H. Koos Zwinderman.

7.6 Safety and Tolerability Evaluations

7.6.1 General Considerations

Safety evaluations will be conducted at screening, at clinic check-in, periodically throughout study conduct, and at the EOS evaluation. See Table 5.1: Visit and Assessment Schedule for the details of evaluation time points. All safety assessments, including but not limited to AEs, clinical laboratory evaluations, vital signs, 12-lead ECG results, physical examination will be listed and where appropriate summarized with descriptive statistics.

7.6.2 Safety and Tolerability Variables

The safety variables to be presented are:

- Physical examination
- Overall asthma symptoms (visual analogue scale (VAS))
- Clinical signs/symptoms reporting (MedDRA)

- (S)AEs
- Vital signs (heart rate (HR), blood pressure (BP), temperature, peripheral oxygen saturation (SpO2))
- Lung function measurements (FEV_1, FEV_1/FVC, Peak Expiratory Flow (PEF), IOS)
- ECG
- Clinical safety laboratory outcomes (e.g. blood: hematology, chemistry, clotting parameters and urinalysis)

The safety set will be used.

7.6.3 Analysis of Safety and Tolerability Endpoints

7.6.3.1 Adverse Events

Treatment-emergent AEs (TEAEs) are defined as AEs that temporally associated with the use of a study drug, whether or not considered related to the study drug. Non-TEAEs (i.e., the pretreatment AEs) are defined as AEs occurring prior to the first dosing. These events will be presented in the listings only and are not included in a summary of AEs.

AEs will be classified as either related or not related to study drug. A study drug-related AE is defined as any TEAE that is assessed to have 'Definite', 'Probable' or 'Possible' relations to study drug. An AE not related to study drug is defined as any AE that is assessed as 'Unlikely' or 'Unrelated' to study drug.

Adverse event data will in addition be coded with the latest version of the MedDRA coding system used before DBL: this is version 25.1 or higher. The SAS programmer or Data Manager of the study will add the coding (using the MedDRA system and SAS) to the AE descriptions extracted from the database.

The TEAEs are tabulated by system organ class (SOC) and preferred terms (PT) within each SOC according to the MedDRA terminology list. They will be tabulated broken down by treatment. TEAEs will be summarized in descending order according to incidence of SOC and PT, using the number and percentage of subjects experiencing a TEAE, as well as the number of events. A subject will be counted once if the subject experiences the same AE more than once with continuous dates.

Adverse events will also be tabulated by intensity and by relationship to study drug. Summary tables will be accompanied by individual subject listings.

If applicable, the same tabulations and listings will be presented for SAEs.

AE duration will be added in the AE listings as 'xDxHxM'; study day will be added in the AE listings as 'Day x' for TEAEs or as 'Prior' for non-TEAEs.

The following calculations and derivations will be used, making the most conservative judgment.

For duration of AE:

- Duration = resolution date and time minus onset date and time.

- If onset or resolution time unknown, then the duration will be calculated based on resolution date and onset date only, and 1 day is added.
- If onset or resolution date is unknown, duration will be missing.

For study day (time to onset) of AE:

- Study day = onset date minus date of the first dose administration, and 1 day is added when onset date and time of event is on or later than the date and time of dose administration.
- Study day will be set to "Prior" if onset date and time of the event is earlier than the date and time of the first dose administration.
- If onset or resolution date is unknown, study day will be missing.

This summary will present the numbers and percentages of subjects according to the following categories:

- Subject with Any TEAE
- Subject with Any TESAE
- Intensity
- Serious AE
- Action Taken
- Treatment Required
- Relationship to Study Drug
- Outcome

Other summary tables for AEs will include:

- Treatment-Emergent Adverse Events – MedDRA
- Treatment-Emergent Adverse Events by Intensity – MedDRA
- Treatment-Emergent Adverse Events by Relationship to Study Drug – MedDRA
- Treatment-Emergent Adverse Events – MedDRA (Preferred Term over XX%)
- Treatment-Emergent Serious Adverse Events – MedDRA
- Treatment-Emergent Serious Adverse Events by Intensity – MedDRA
- Treatment-Emergent Serious Adverse Events by Relationship to Study Drug – MedDRA
- Listing of Subjects with Treatment-Emergent Serious Adverse Events
- Listing of Subjects Who Discontinue Due to Treatment-Emergent Adverse Events
- Listing of Subjects Who Dead Due to Treatment-Emergent Adverse Events

7.6.3.2 Treatment Exposure and Compliance

The records of study drug administered during the course of study will be listed and summarized with the following parameters by treatment for checking the compliance:

- Total Planned Dose (Cap)
- Total Dose Received (Cap)
- Total Dose Missed (Cap)
- Duration on Study Treatment (Days)
- Compliance (%)
- <80%
- 80%~120%

The following statistics will be provided in the table: number of subjects (n), mean, SD, median, minimum and maximum.

For compliance of study drug administration:

- Compliance (%) = total dose received / total planned dose during the participated study period days * 100%

7.6.3.3 Clinical Laboratory Evaluations

Laboratory parameters to be determined per protocol are:

Hematology	Chemistry	Urinalysis	Others
Hemoglobin Hematocrit RBC count Platelet count WBC count Neutrophils (total) Eosinophils Monocytes Basophils Lymphocytes Mean corpuscular volume (MCV)	BUN Creatinine Fasting glucose Sodium Potassium ALT AST GGT Bilirubin (total, direct and indirect) Alkaline phosphatase Albumin Cholesterol (total) LDL HDL Triglycerides Lactate dehydrogenase Total protein	Urobilinogen Nitrites pH Glucose[a] Protein[a] Blood[a] Ketones[a] Microscopy[b] Specific gravity Bilirubin Leukocytes	Serum HDM-specific IgE Serum pregnancy test[c] FSH[d] Serology (HIV, hepatitis B and hepatitis C)[e] Coagulation (PT, INR, PTT, thrombocytes) Urine drug screen Alcohol breath test Cotinine test

[a] Dipstick.
[b] Only if urine dipsticks is positive for blood or protein.
[c] Only during screening, other pregnancy tests will be done with urine.
[d] Required of postmenopausal females only during screening.
[e] Only at Screening.

All qualitative laboratory data will be supplied per lab manual, which is checked on the use of SI units by clinic and (if necessary) converted to SI units for the descriptive statistics.

Listings will only present the original values, units and reference ranges as received from the laboratory.

Laboratory safety data collected according to protocol will be summarized and listed according to protocol scheme time. Change from baseline for hematology, chemistry and urinalysis will be calculated and summarized as well. The judgment including ‘Normal’, ‘Abnormal NCS’, and ‘Abnormal CS’ from baseline over time will be summarized as a shift table.

Listings will be created of the laboratory data according to protocol, including extraneous laboratory data, if applicable. Listings of all clinical laboratory data for each subject will be provided

with values outside the normal ranges or abnormal indicated. Both the PI judgement as well as the laboratory judgement will be added in the listing.

7.6.3.4 Vital Signs

Vital signs (HR, respiratory rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), body temperature, SpO2) collected according to protocol will be summarized using descriptive statistics for each scheme time. Change from baseline over time will be calculated and summarized as well.

Listings of all vital sign data will be provided.

7.6.3.5 12-lead ECG

ECG interval data (HR, RR, PR, QRS, QT and QTc (Bazett and Fridericia)) collected according to protocol will be summarized using descriptive statistics for each time point. Change from baseline over time will be calculated and summarized as well. For the screening ECG and the baseline ECG, three recordings will be made with a 1-minute interval between recordings. For the evaluation of the corrected QT intervals, the average of the 3 recordings will be taken as baseline. All other recordings will be single (one recording of at least 3 complexes).

All individual ECG interval data and assessments will be listed.

7.6.3.6 Physical Examination

Results of physical examinations conducted throughout the study will be presented in listings, and the observed result will be summarized in summary table.

7.6.3.7 Lung Function Measurements

Lung function measurements (FEV_1, FEV_1/FVC, PEF, IOS (including R5, R20, R5-R20, Fres, X5, and AX)) collected according to protocol will be listed only. The summary table of spirometry and IOS parameters will be provided in the PKPDAP.

7.6.3.8 Overall Asthma Symptoms (VAS)

VAS scale collected according to protocol will be summarized using descriptive statistics for each scheme time. Change from baseline over time will be calculated and summarized as well.

8 CHANGES FROM PROTOCOL AND OTHER REMARKS

There were no significant changes to the analyses planned in the study protocol.

9 SOFTWARE

9.1 Coding Systems

Adverse events, Medical History and Concomitant Medication will be coded as described in the Data Management documentation.

9.2 Statistical Software

The statistical analysis and reporting will be done using SAS for Windows™ version 9.4 or higher. SAS output will be saved and imported into Word®.

9.3 Reporting

All safety output will be generated as SAS tables and listings. All tables and listings will be created such that they fit landscape pages. All tables and listings will be created using SAS with an PDF output, and font Times New Roman in size 9 will be used.

A list of tables and listings is presented (per report section) in Section 10.

The QPS template tables and listings will be used, and a separate templates document will be supplied together with the SAP. Adaptations to template layout are possible depending on the design of the study, the length of variables and the number of variables. It should be noted that all data as collected will be presented in listings and/or tabulations. The examples in the templates document may not cover all possible collected data, or examples may be present of data not collected for this specific study.

All tables and listings created will need to adhere to the following margins to fit the appendix layout if the clinical study report (CSR):

Landscape: Top - 0.75 inch
Bottom - 0.375 inch
Left - 0.375 inch
Right - 0.375 inch

10 TABLES, LISTINGS AND FIGURES

10.1 List of Tables and Figures – core text

All tables and graphs mentioned here will be presented in the report, and will be supplied to the Medical Writer as separate .RTF or .DOCX files.

- Summary table of subject disposition: Frequency and percentage.
- Summary table of demographic data, including weight, height, BMI, blood eosinophils, $PC20FEV_1$(Meth) or $PC20FEV_1$(Hist) and FEV_1 in % predicted value at screening, for all-

treated set: Mean, SD, minimum, median, and maximum for quantitative variables. Frequency and percentage for qualitative variables.

- Summary table presenting the results of the statistical model.

- Adverse event summary containing the number and percentage of subjects experiencing any TEAE or TESAE. Summary table will contain information concerning the intensity and relationship, and discontinuation due to an AE.
- Adverse event summary containing the number and percentage of subjects experiencing TEAEs. AEs are tabulated by MedDRA SOC and PT, and summarized by treatment group. AEs will be summarized alphabetically by SOC and descending order according to incidence of PT.

- If applicable, the same tabulations will be presented for SAEs.

- If applicable: summary listing of SAE containing description of event, MedDRA preferred term, subject number, relationship, action taken and outcome.

10.2 List of Tables – end of text

All tables mentioned here will be presented according to ICH guidelines in appendix 14 of the report. A complete document (batch load) will be created in Word for the Medical Writer, in the order and with section number and title as stated.

14.1 Demographic Data Summary figures and tables
14.2 Efficacy Data Summary figures and Tables
14.3 Safety Data Summary figures and tables
- 14.3.1 Displays of Adverse Events
- 14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events
- 14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events
- 14.3.4 Abnormal Laboratory Value Listing (each subject)

Section	Title	Notes
14.1.1	Summary of Subject Disposition	Summary of all randomized, completed study, primary reason for discontinuation, and the number of subjects in the all-treated set, safety set, and per-protocol set per sequence group.
14.1.2	Summary of Demographics	Descriptive statistics for demographics per sequence group.
14.1.3	Summary of Drug Compliance	Descriptive statistics for the parameters of total planned dose, total dose received, total dose missed, duration on study treatment, compliance (%) as well as count and percentage of subjects with compliance <80% or within 80%~120% per treatment.
14.3.1.1	Treatment-Emergent Adverse Events	Adverse event summary containing the number and percentage of subjects experiencing any TEAE or TESAE. Table will

		contain information of serious AE (yes or no), action taken, treatment required (yes or no), relationship to study drug, and outcome. Table will be presented per treatment and all subjects combined.
14.3.1.2	Treatment-Emergent Adverse Events - MedDRA	Adverse event summary containing the number and percentage of subjects experiencing TEAEs. TEAEs are tabulated by SOC and PT, and summarized by treatment and all subjects combined.
14.3.1.3	Treatment-Emergent Adverse Events by Intensity - MedDRA	The same tabulation as 14.3.1.2 will be created for TEAEs by intensity.
14.3.1.4	Treatment-Emergent Adverse Events by Relationship to Study Drug - MedDRA	The same tabulation as 14.3.1.2 will be created for TEAEs by relationship to study drug.
14.3.1.5	Treatment-Emergent Adverse Events - MedDRA (Preferred Term over XX%)	Summary containing the number and percentage of PT occurred over XX% per treatment and all subjects combined. (XX% will be determined based on the actual data)
14.3.1.6	Treatment-Emergent Serious Adverse Events - MedDRA	The same tabulation as 14.3.1.2 will be created for TESAEs.
14.3.1.7	Treatment-Emergent Serious Adverse Events by Intensity - MedDRA	The same tabulation as 14.3.1.2 will be created for TESAEs by intensity.
14.3.1.8	Treatment-Emergent Serious Adverse Events by Relationship to Study Drug - MedDRA	The same tabulation as 14.3.1.2 will be created for TESAEs by relationship to study drug.
14.3.2.1	Listing of Subjects with Treatment-Emergent Serious Adverse Events	Listing all TESAE.
14.3.2.2	Listing of Subjects Who Discontinue Due to Treatment-Emergent Adverse Events	Listing the subjects who withdraw due to TEAE.
14.3.2.3	Listing of Subjects Who Dead Due to Treatment-Emergent Adverse Events	Listing the subjects who expire due to TEAE.
14.3.4	Abnormal Laboratory Values for All Subjects	A subject listing of all laboratory values outside the (investigators) reference range, containing the parameters, sex, age, collection date/time, value, reference range, flag, and whether there were clinically significant (NCS/CS).
14.3.5.1 – 14.3.5.3	Summary of Clinical Laboratory – Hematology/ Chemistry/ Urinalysis	Descriptive statistics for absolute value and change from baseline by scheme time point per treatment and all subject combined.
14.3.5.4 – 14.3.5.6	Individual Subject Changes (Shift Table) – Hematology/ Chemistry/ Urinalysis	Shift table for laboratory data per treatment.
14.3.6-14.3.9	Summary of Vital Signs/ Physical Examination/ Overall Asthma Symptoms (VAS)	Descriptive statistics for absolute values and change from baseline by scheme time point per treatment and all subjects combined. Summary of overall asthma symptoms (VAS) will be presented per treatment only.

Full details are provided in SAP Mock Table.

10.3 List of Subject Data Listings

All listings mentioned here will be presented according to ICH guidelines in Appendix 16.2 of the report. A complete document ("batch load") will be created in Word for the Medical Writer, in the order and with section number and title as stated.

16.2 Subject data listings
- 16.2.1 Discontinued subjects
- 16.2.2 Protocol deviations
- 16.2.3 Subjects excluded from the efficacy analysis
- 16.2.4 Demographic data
- 16.2.5 Compliance and/or drug concentration data
- 16.2.6 Individual efficacy response data
- 16.2.7 Adverse event listings
- 16.2.8 Listing of individual laboratory measurements by subject

16.4 Individual Subject Data Listing

Individual listings will be prepared of all the data collected in the database. No combining of data other than mentioned in this paragraph will be performed. Listings will be presented per treatment/sequence. The key variables in all listings will be subject number and treatment/sequence. If applicable, period/visit number, day and time point will be listed additionally. For laboratory data, set and age will be added to the listing, if deemed relevant. For AE data, duration, and study day (time to onset) will be added.

Section	Title	Notes
16.2.1.1	Subjects Disposition (Date of Visit)	
16.2.1.2	Subjects Disposition (Complete Status)	
16.2.1.3	Subject Who Did Not Meet Criteria	
16.2.1.4	Allergy Testing (Serum IgE Level)	
16.2.1.5	Allergy Testing (Skin Prick Test)	
16.2.2	Protocol Deviations	
16.2.3	Subjects Excluded from the Analysis	Including all-treated set, safety set and per-protocol set
16.2.4.1	Individual Subject Demographics	
16.2.4.2 – 16.2.4.3	Medical History of Asthma/ Allergy	
16.2.4.4	Medical/ Surgery History	Including MedDRA coding
16.2.4.5	Prior Medication	Including WHODrug Global coding
16.2.4.6	Concomitant Medication	Including WHODrug Global coding
16.2.4.7 – 16.2.4.8	Clinical Laboratory Test – Follicle Stimulating Hormone (FSH)/ Virus Serology	
16.2.5.1	Randomization	
16.2.5.2	Study Drug Administration	
16.2.5.3	Salbutamol Administration	
16.2.5.4	Un-Blind	
16.2.5.5	Individual Blood Sampling of FP-025	Including scheduled and actual scheme times
16.2.6.1	Inhaled Allergen (HDM) Challenge	
16.2.6.2	Methacholine Challenge	

16.2.6.3	Sputum Induction for Methacholine	
16.2.6.4	Impulse Oscillometry System (IOS)	Extraneous data
16.2.6.5	Spirometry	Extraneous data
16.2.6.6	Overall Asthma Symptoms (VAS)	
16.2.6.7	Fractionated Nitric Oxide (FeNO) in Exhaled Air	
16.2.6.8	Exhaled Breath Condensate (EBC)	
16.2.6.9	Nasal Lavage (NAL) and Nasal Brush (NAB)	
16.2.6.10	Blood Collection for Inflammation Markers, Biomarker and PBMC Sample	
16.2.6.11	Urine Collection for Biomarker	
16.2.7	Individual Subjects Adverse Events	
16.2.8.1 – 16.2.8.8	Clinical Laboratory Tests – Hematology/ Chemistry/ Urinalysis/ Microscopy/ Urine Pregnancy Test/ Urine Drug Screen/ Alcohol Breath Test/ Cotinine Test	Including extraneous data and comments
16.4.1 – 16.4.3	Individual Subject Vital Signs/ Physical Examination/ 12-Lead ECG	

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Jo Chen jo.chen@qps.com Senior Manager of Biostatistics QPS Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 23D5E8B8-86CE-45B0-8E33-FCB846C93080 Using IP Address: 223.140.150.42 Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 03-30-2023 | 21:04 Viewed: 03-30-2023 | 21:47 Signed: 03-30-2023 | 21:48
Electronic Record and Signature Disclosure: Accepted: 09-07-2020 | 16:59 ID: 752440e9-9ba1-4e74-a9b8-7546896b3304		

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Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	03-30-2023 | 20:34
Certified Delivered	Security Checked	03-30-2023 | 22:44
Signing Complete	Security Checked	03-30-2023 | 22:45
Completed	Security Checked	03-30-2023 | 22:45
Payment Events	**Status**	**Timestamps**
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Disclosure Preview

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By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

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- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify QPS as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by QPS during the course of your relationship with QPS.