STATISTICAL ANALYSIS PLAN

FINAL VERSION 03.00, 17 NOVEMBER 2023

A Phase 1, Randomized, Double-blind, Placebo-controlled, Multiple Ascending Dose Study to Assess the Safety, Tolerability, Immunogenicity, Pharmacokinetics and Pharmacodynamics of UPB-101 in Subjects with Asthma

UPB-CP-01

Prepared by: S-cubed Biometrics Ltd.

For: Upstream Bio

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1. STATISTICAL ANALYSIS PLAN APPROVAL FORM

	Signature	Date (ddmmmyyyy)	Time (hh:mm)	Local Time Zone
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3. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACQ-7	Asthma Control Questionnaire-7
ADA	Anti-Drug Antibody
AE	Adverse event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine transaminase
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUC	Area under the curve
BDRM	Blinded data review meeting
β-HCG	Beta human chorionic gonadotropin
BLQ	Below level of quantification
BMI	Body mass index
BP	Blood pressure
Bpm	Beats per minute
CGI-C	Clinicians Global Impression of Change
CI	Confidence Interval
CRF	Case Report Form
CRP	C-reactive protein
CSR	Clinical Study Report
DBP	Diastolic blood pressure
ECG	Electrocardiogram
FeNO	Fractional exhaled nitrous oxide
FEV1	Forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
GM	Geometric Mean
GSD	Geometric Standard Deviation
HbsAg	Hepatitis B surface antigen
HCAb	Hepatitis C antibodies
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HR	Heart Rate
ICF	Informed Consent Form
IFN	Interferon
IgE	Immunoglobulin E
IL-	Interleukin-
INR	International Normalized Ratio
IP-10	Interferon gamma-induced protein 10
IV	Intravenous
IMP	Investigational medicinal product

Abbreviation	Definition
LLOQ	Lower Limit of Quantification
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralising Antibody
PD	Pharmacodynamic
PEF	Peak Expiratory Flow
PI	Principal Investigator
PK	Pharmacokinetic
pSTAT	Phosphorylated signal transducer and activator of transcription
PT	Prothrombin time
PT	Preferred Term
Q1	Lower Quartile
[redacted]	every [redacted] weeks
[redacted]	every [redacted] weeks
[redacted]	every [redacted] weeks
QTc	QT interval corrected
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
Q3	Upper Quartile
RR	Respiratory rate
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
SRC	Safety Review Committee
TARC	thymus activation regulated chemokine
TB	Tuberculosis
TEAE	Treatment emergent adverse event
TFL	Tables, Figures and Listings
TSLP	thymic stromal lymphopoietin
ULN	upper limit of normal
WBC	White blood cell
WHO	World Health Organisation

4. INTRODUCTION

This statistical analysis plan (SAP) explains in detail the statistical analyses that will be performed for the Upstream Bio UPB-CP-01 study. The study is sponsored by Upstream Bio and being conducted in partnership with tranScrip. The analysis is outlined within the study protocol V8.0, dated 17 Jan 2023, and this SAP contains a more technical and detailed description of those analyses outlined in the protocol. In particular, information is provided on the definitions of the study populations, and it also details the list of Tables, Figures and Listings (TFL) that will be produced by S-cubed Biometrics for use and inclusion with the Clinical Study Report (CSR).

This SAP provides a detailed description of the analyses that will be undertaken at the time of each analysis and has been written and finalised before the statistical and programming teams are unblinded for the Primary (Week 24) Analysis. The Sponsor personnel are unblinded throughout the study and so their involvement in any changes to the statistical analysis specified in the SAP beyond the first draft will be documented in an appendix to the final SAP.

A Blinded Data Review Meeting (BDRM) will be conducted when the study is complete (all subjects have completed Week 32 visit) and data is cleaned, prior to final database lock.

Additionally, an unblinded administrative interim analysis will take place prior to the Primary Analysis. The outputs and analyses required for the administrative interim analysis are described in this SAP also.

Any deviations from the protocol specified analyses will be listed in Section 11, and any deviations from the analyses stated within this SAP, will be described within the CSR.

Below is a summary of the protocol updates, any changes required to the statistical analysis plan (SAP) as a result of these changes have been incorporated as appropriate.

Following MHRA/REC review, Version 4.0 was created which updated the inclusion criteria and restrictions related to pregnancy and contraception, increased the frequency of symptom driven physical examinations and amended the wording around stopping criteria and restarting the trial. Version 5.0 made a number of non-substantial changes to the protocol:

- Correction to order of assessments to allow blood draws to occur earlier in the visit to minimise diurnal variations in the level of eosinophils.
- Corrections/clarifications to timing of PK/PD assessments to be conducted between 6 AM and 10 AM. Spirometry assessments are excluded from the 6 – 10 AM time window to allow them to be collected at appropriate times relating to other assessments/dosing.
- Clarification that requirement for contraception for female subjects only applies when engaging in sexual activity with a male partner. Clarification that males who have a partner of child-bearing potential must either be sterile or their partner must use contraception.
- Clarification that the Screening Period is defined as Day -21 to Day -1.
- Addition of explicit statement to allow procedures for Visit 1 to be conducted across multiple days.
- Correction to Schedule of Events Table 6, Table 7 and Table 8. COVID testing added for Day 78 for [redacted] and [redacted] cohorts and for Days 127 and 155 for [redacted] cohorts.
- Correction to Schedule of Events, Table 7. Samples for future analysis of additional cytokines added for [redacted] cohorts, Day 10.
- Correction to Schedule of Events, Table 8. Visit window of ±3 days added for D127 and D155 for [redacted] cohorts.

- Clarification that on days where Spirometry is not performed, ACQ-7 question 7 will be completed by the investigator based on the FEV1 value from the first measurement on the following morning.
- Clarification/Correction to assessment of Asthma Clinical Global Impression of Change (CGI-C). CGI-C is an assessment of the change vs. baseline (Day -1) and is therefore not required on or prior to Day -1.
- Clarification for repeating of tests that may be remedied with time when enrolment criteria are initially failed.
- Clarification for Future Cohort Eligibility allowing rescreening of subjects who failed eligibility due to potential diurnal variations in eosinophil levels drawn after 11 am.
- Clarification to Clinical Laboratory Assessments stating that eosinophil data will be provided to sites during screening but not afterwards. Addition of requirements for monocytes and basophils data obtained after screening to not be provided to any blinded parties including site personnel in order to remove the possibility of eosinophil data being calculated.
- Clarification that blinded site personnel may dose subjects provided all of the blinding conditions are met.
- Clarification to management of Emergency Unblinding of Treatment Assignment. The Investigator is encouraged to discuss options with the blinded Medical Monitor and to notify the blinded Medical Monitor as soon as possible.
- Clarification for process of delivery of liver safety monitoring alerts from central laboratory and assessment of the parameters by the Investigator (Appendix 1).
- Correction of all references to Plasma UPB-101 concentrations to Serum UPB-101 concentrations.
- Correction to remove “serum” in all instances of total IgE measurements.

Version 6.0 was another non-substantial amendment which updated the following:

- Adjustment to the acceptable upper age limit from 55 to 60 years.
- Modification to the eosinophils requirement during the Screening Period, allowing for participants with eosinophil count ≥150 and <200 cells/µL to be considered in instances where their fractional exhaled nitric oxide (FeNO) is greater than 25 parts per billion (ppb) at either Visit 1 or Visit 2.
- Removal of the requirement for participants to be fully vaccinated against SARSCoV-2 (Coronavirus disease 2019 [COVID19]).
- Expansion of the window for later visits from +/- 3 to +/- 5 day.
- Replacement of the blinded medical monitor’s contact telephone number with a 24/7 telephone call cascade number.

Version 7.0 was a substantial protocol amendment and updated:

- Removal of language specifying cohort enrolment as parallel-sequential in nature. This change enables enrolment into Cohort 3 following partial enrolment into Cohort 2 due to the temporary halt to dosing.
- Updates to language related to Safety Review Committee which according to the original protocol would have been convened only between the second and third doses of Cohorts 1 and 2.

Version 8.0 was a non-substantial amendment and updated:

- Addition of timepoints for evaluation of the pharmacodynamic (PD) effect of UPB-101 biomarkers, specficially, the fractional exhaled nitric oxide (FeNO) and blood eosinophil numbers to participants enrolled in Cohort 4.
- Specification of the dose level and regimen to be administered to participants enrolled in Cohort 4.

- Extension of the estimated study end date to October 2023.

5. STUDY OBJECTIVES

5.1. Primary Objective(s)

To assess the safety and tolerability of UPB-101 when administered as multiple ascending doses.

5.2 Secondary Objective(s)

To assess the immunogenicity of UPB-101 when administered as multiple ascending doses.

To characterize the pharmacokinetics (PK) of multiple ascending doses of UPB-101.

5.3 Exploratory Objective(s)

To assess 32-week **extended** safety and tolerability of UPB-101 when administered as multiple ascending doses.

To assess 32-week **extended** immunogenicity of UPB-101 when administered as multiple ascending doses.

To characterize 32-week **extended** PK of multiple ascending doses of UPB-101.

To assess the pharmacodynamic (PD) effect of UPB-101 on biomarkers related to asthma and/or the thymic stromal lymphopoietin (TSLP) pathway.

To assess the PD effect of UPB-101 on clinician and subject impression of overall asthma severity.

To explore the PD effect of UPB-101 on lung function.

6. STUDY DESIGN

6.1. Summary of Study Design

This is a two-part Phase 1, multi-centre randomized, double-blind (Investigator and Subject blinded; Sponsor unblinded), placebo-controlled, multiple ascending dose study to assess the safety, tolerability, immunogenicity, PK, and PD of UPB-101 administered subcutaneous (SC) to adult subjects with asthma.

The study consists of Part A and Part B. Part A includes 3 cohorts with pre-set dosing regimens. Part B includes 2 adaptive design cohorts whose doses and dosing intervals will be decided based upon the safety, PK, and PD results from Part A available to the unblinded Sponsor. The regimens selected for Part B will not exceed the exposures (i.e., doses and/or dosing intervals) included in Part A.

The study will consist of 5 parallel-sequential cohorts: 3 cohorts in Part A and 2 cohorts in Part B. Eight subjects will be randomized per cohort (6 active, 2 placebo). The term 'parallel-sequential cohorts' means that the first 8 subjects will be randomized to Cohort 1. As soon as quota for Cohort 1 has been filled, Cohort 2 will be open to enrolment and so forth. A total of approximately 40 subjects will be enrolled in the study with 24 subjects in Part A and 16 in Part B.

The study includes 4 periods: Pre-Screening, Screening, Dosing, and Observation.

Pre-screening Period: Sites may opt to utilize a Pre-screening Informed Consent Form (ICF) to enable performance of a complete blood count (for the absolute eosinophil numbers) in consenting subjects while subjects consider consent for the full study. Pre-screening may not occur more than 90 days before Visit 1.

Screening Period: Subjects will be evaluated for eligibility during the 21-day Screening Period before randomization and dosing. Eligible subjects will be allocated to cohorts sequentially and then be randomly allocated to treatment with UPB-101 or placebo in a 3:1 ratio, respectively.

Dosing Period: Study drug will be administered SC as follows:

Description of SC Dosing Regimens in Part A			
Cohort	**Treatment Arm and Dosage**	**Number of Injections to Achieve Dose**	**Frequency x Number of Doses**
Cohort 1	UPB-101 [redacted] mg Placebo	[redacted]	[redacted]
Cohort 2	UPB-101 [redacted] mg Place[redacted]	[redacted]	[redacted]
Cohort 3	UPB-101 [redacted] mg Place[redacted]	[redacted]	[redacted]
Description of SC Dosing Regimens in Part B (Adaptive Design)			
Cohort 4	UPB-101 [redacted] mg Placebo	[redacted]	[redacted]
Cohort 5	UPB-101	[redacted] mg [redacted], or [redacted]	
	Placebo	**OR** [redacted] mg [redacted] (repeated)	

[redacted] = every [redacted] weeks; [redacted] = every [redacted] weeks; [redacted] = every [redacted] weeks; SC = subcutaneous

Subjects will be admitted to the inpatient area of their site the day before each dosing day. After each administration of the study drug, subjects will be monitored in the site for a minimum of 4 hours to assure their safety.

Observation Period: Following their final dose administration, subjects will be followed for evaluation of safety, PD, PK, and immunogenicity monitoring. Subjects enrolled in cohorts with [redacted] or [redacted]

dosing intervals will be observed for 6 months; subjects enrolled in any cohorts with [redacted] dosing intervals will be observed for 5 months.

All PD and PK assessments will be conducted between 6 AM and 10 AM to minimize the impact of diurnal variations on biomarker assessments.

6.1.1. Safety Review Committee

Part A

Subjects in Cohorts 1 and 2 will receive 3 doses of study drug. Before the first subject in each of those cohorts receives their third dose, the Safety Review Committee (SRC) will be convened. The committee will review at each of the meetings the safety data available at that point in time from all enrolling cohorts.

Subjects enrolled in Cohort 3 will receive only 2 doses of the study drug. Therefore, no SRC meetings will be directly linked to the progress of that cohort.

The blinded safety data reviewed will include AEs, vital signs, physical examinations, ECGs, haematology, biochemistry, urinalyses, as well as subject withdrawals and replacements. Eosinophil data will not be sent to sites or reviewed by the SRC.

Following this data review, the SRC will report their safety findings and make a recommendation whether the third dosing in the current cohort should proceed as planned or be modified (e.g., repeated or reduced), paused, or halted.

Part B

Study drug exposures in Cohorts 4 and 5 will not exceed the exposure of any of the cohorts in Part A. Therefore, no SRC meetings are scheduled for Part B.

Administrative Interim Analysis

An administrative interim analysis will be conducted during Q4 of 2022. This will be unblinded and will be undertaken by a team who will have no other involvement in the study until after unblinding. The data and results will be kept in a restricted area which will only be accessible by this unblinded team. The results will be made available to the sponsor via a secure transfer service.

This interim is solely for internal decision-making pertaining to matters unrelated to the current study, UPB-CP-01, and so will have no bearing on the continued conduct and/or analysis of the study.

6.2. Randomisation and Blinding

Subjects will be randomized by IXRS in a double-blind fashion to either UPB-101 or matching placebo in a 3:1 ratio. Each subject will be assigned a randomization number by IXRS which will correspond to the treatment and cohort allocation. Subjects, Investigators, all site personnel (except for the designated unblinded dispensing pharmacist and flow cytometry laboratory personnel) and the tranScrip team will be blinded to the subjects' allocations.

The following procedures have been instituted to mitigate the risk of unbinding of the enrolled subjects and blinded site personnel during the study drug administration:

- Qualified study personnel situated in the isolated site pharmacy will prepare the solutions for injection based upon the randomization allocation;

The study drug and matching placebo will be identical (or nearly identical) in appearance once drawn into the syringe for injection;

All the prepared syringes will be covered with blinding labels;

Subjects will be dosed by site personnel trained in blinding techniques and instructed not to discuss the subjects' study drug assignments with blinded site personnel;

Subjects will be dosed in a cordoned area out of the view of the blinded site personnel and of other study subjects.

The Sponsor will be unblinded throughout this exploratory study but will not be involved directly in the treatment or clinical evaluation of the subjects.

All potentially unblinded roles and unblinding parameters within the study will be documented separately and a risk assessment performed to ensure appropriate processes are in place to maintain the blind throughout the blinded period of the study.

Since PK data and some PD assessments from individual subjects may be unblinding, such data will be available to the unblinded Sponsor but not to any of the blinded parties. Therefore, until the entire study (i.e., Parts A and B) has been concluded and the database locked, results of eosinophil numbers, FeNO, total IgE, CRP, cytokines, and TSLP will be accessible only to unblinded parties. Summary analyses of the overall PK data will be reported to the SRC. These reports will not contain any unblinded individual PK results.

A blinded Medical Monitor will be assigned to support site communications regarding specific subjects and adverse events, assignment of Sponsor causalities and other activities that will be described in the medical monitoring plan.

6.3. Time and Events Schedule

Table 1: Schedule of Screening Assessments for All Cohorts

Study Procedures	Visit 1	Visit 2	Visit 3
Study Day	**Day -21 to -5**	**Day -5 (±2)**	**Day -1**
Informed consent	X		
Inclusion/exclusion criteria	X	X	X
Demographics	X		
Medical and surgical histories	X		
Prior Medication History	X	X	X
Pregnancy test [a]	X (urine)	X (serum)	X (urine)
FSH [a]	X		
Viral serology	X		
QuantiFERON®-TB Gold test	X		
Urine drug/nicotine/cotinine screen	X	X	X
Alcohol breath or urine test	X	X	X
Physical examination (full)	X		
Physical examination (symptom-driven)		X[b]	X[b]
Body weight, height, and BMI	X		
Vital signs	X	X	X
12-lead ECG [d]	X	X	X
Blood chemistry [g]	X	X	
Urinalysis	X	X	
FeNO	X	X	
Pulmonary Function Tests (Spirometry) [e]	X	X	
Haematology & eosinophils [f]	X	X	
ACQ-7[h]		X	X
Admission (Ad) or Discharge (Di) from site	[redacted]		
COVID-19 protocol as per site SOPs	X	X	X
Subject contact	(X)	(X)	(X)
Review and record AEs	X	X	X

Table 2: Schedule of Events Day 1 to Day 15 for All Cohorts

	Dosing Period					
Visit	**4**	**5**	**6**	**7**	**8**	**9**
Study Week	**W0**	**W0**	**W0**	**W1**	**W2**	**W3**
Procedures **Study Day**	**D1**	**D2**	**D4**	**D8**	**D15**	**D22**
Visit window (days)	0	0	0	±1	±2	±2
Pregnancy test [a]	X	X	X	X	X	X
Physical examination (symptom-driven)	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
Vital signs [c]	X		X		X	X
12-lead ECG [d]	X		X	X	X	X
Haematology & eosinophils [f]	X	X[m]	X[m]	X	X	
Blood chemistry [g]	X				X	
Urinalysis	X				X	
FeNO	X	X[n]	X[n]	X	X	
Pulmonary Function Tests (Spirometry) [e]	X			X	X	
Total IgE	X				X	
C-reactive protein	X				X	
Biomarkers [j]	X				X	
Future analysis of additional cytokines	X				X	
Flow cytometry [l]	X				X	
CGI-C and ACQ-7 [h]					X	
Serum for PK [i]	X	X	X	X	X	X
Serum ADA and NAbs (immunogenicity)	X					
Randomization	[redacted]					
UBP-101 administration/post-dose observation	[redacted]					
COVID-19 protocol as per site SOPs	X	X	X	X	X	X
Admission (Ad) or Discharge (Di) from site	[redacted]					
Subject contact [k]	(X)		(X)		(X)	
Concomitant medication	X	X	X	X	X	X
Assess injection site reactions	X	X	X	X		
Review/Record AEs	X	X	X	X	X	X

Table 3 Schedule of Events - Cohorts with [redacted] Dosing Interval

	Dosing Period					Observation Period										
Visit	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**
Study Week	**W3**	**W4**	**W5**	**W7**	**W8**	**W8**	**W8**	**W9**	**W10**	**W11**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**
Procedures / Study Day	**D28**	**D29**	**D36**	**D56**	**D57**	**D58**	**D60**	**D64**	**D71**	**D78**	**D85**	**D113**	**D141**	**D169**	**D197**	**D225/ Final Visit**
Visit window (days)	±2	±2	±1	±2	±2	0	0	±1	±2	±3	±3	±5	±5	±5	±5	±5
Pregnancy test [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination (full)																X
Physical examination (symptom-driven)	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	
Body weight																X
Vital signs [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG [d]		X	X		X		X	X	X		X	X	X			X
Haematology & eosinophils [f]		X	X		X				X		X	X	X	X	X	X
Blood chemistry [g]		X	X		X				X		X	X	X			X
Urinalysis		X	X		X				X		X	X	X			X
Total IgE		X			X						X	X	X	X	X	X
C-reactive protein		X			X						X	X	X	X	X	X
FeNO		X			X						X	X	X	X	X	X
Pulmonary Function Tests (Spirometry) [e]		X			X						X	X	X	X	X	X
Biomarkers [j]		X			X						X	X	X	X	X	X
Future analysis of additional cytokines		X			X						X	X	X	X	X	X
Flow cytometry [k]		X			X						X	X	X	X	X	X
CGI-C and ACQ-7 [h]	X			X							X	X	X	X	X	X
Serum sample for PK [i]	[redacted]															
Serum ADA and NAbs (immunogenicity)																
Study drug administration																
COVID-19 protocol per site SOPs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
4-hour post-dose observation	[redacted]															
Admission (Ad)/Discharge (Di)																
Subject contact [k]		(X)	(X)		(X)		(X)		(X)		(X)	(X)	(X)	(X)	(X)	(X)
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Assess injection site reactions	[redacted]															
Review/Record AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 4 Schedule of Events - Cohorts with [redacted] Dosing Interval

	Dosing Period				Observation Period										
Visit	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Study Week	**W4**	**W6**	**W7**	**W8**	**W8**	**W8**	**W9**	**W10**	**W11**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**
Procedures **Study Day**	**D29**	**D43**	**D56**	**D57**	**D58**	**D60**	**D64**	**D71**	**D78**	**D85**	**D113**	**D141**	**D169**	**D197**	**D225/Final Visit**
Visit window (days)	±2	±2	±2	±2	0	0	±1	±2	±3	±3	±3	±3	±3	±3	±3
Pregnancy test [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination (full)															X
Physical examination (symptom-driven)	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	
Body weight															X
Vital signs [c]	X	X	X	X		X		X	X	X	X	X	X	X	X
12-lead ECG [d]	X			X		X	X	X	X	X	X	X			X
Haematology & eosinophils [f]	X			X						X	X	X	X	X	X
Blood chemistry [g]	X			X						X	X	X			X
Urinalysis	X			X						X	X	X			X
Total IgE	X			X						X	X	X	X	X	X
C-reactive protein	X			X						X	X	X	X	X	X
FeNO	X			X						X	X	X	X	X	X
Pulmonary Function Tests (Spirometry) [e]	X			X						X	X	X	X	X	X
Biomarkers [ij]	X			X						X	X	X	X	X	X
Future analysis of additional cytokines	X			X						X	X	X	X	X	X
Flow cytometry [l]	X			X						X	X	X	X	X	X
CGI-C and ACQ-7 [h]	X		X							X	X	X	X	X	X
Serum samples for PK [hi]	[redacted]														
Serum ADA and NAbs (immunogenicity)															
Study drug administration	[redacted]														
COVID-19 protocol per site SOPs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
4-hour observation (post-dose)	[redacted]														
Admission (Ad) and Discharge (Di)															

	Dosing Period				Observation Period										
Visit	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Study Week	**W4**	**W6**	**W7**	**W8**	**W8**	**W8**	**W9**	**W10**	**W11**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**
Procedures **Study Day**	**D29**	**D43**	**D56**	**D57**	**D58**	**D60**	**D64**	**D71**	**D78**	**D85**	**D113**	**D141**	**D169**	**D197**	**D225/Final Visit**
Subject contact [jk]	(X)	(X)		(X)		(X)		(X)		(X)	(X)	(X)	(X)	(X)	(X)
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess injection site reactions															
Review/Record AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 5 Schedule of Events - Cohorts with [redacted] Dosing Interval

	Dosing Period						Observation Period										
Visit	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
Study Week	**W4**	**W6**	**W8**	**W10**	**W11**	**W12**	**W12**	**W12**	**W13**	**W14**	**W16**	**W18**	**W20**	**W22**	**W24**	**W28**	**W32**
Procedures / Study Day	**D29**	**D43**	**D57**	**D71**	**D84**	**D85**	**D86**	**D88**	**D92**	**D99**	**D113**	**D127**	**D141**	**D155**	**D169**	**D197**	**D225 Final Visit**
Visit window (days)	±3	±3	±3	±3	±2	±2	0	0	±1	±1	±2	±5	±5	±5	±5	±5	±5
Pregnancy test [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination (full)																	X
Physical examination (symptom-driven)	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	
Body weight																	X
Vital signs [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG [d]	X		X			X		X	X	X	X		X		X	X	X
Haematology & eosinophils [f]	X		X			X	X [m]	X [m]	X [m]	X [m]	X		X		X	X	X
Blood chemistry [g]	X		X			X					X		X		X	X	X
Urinalysis	X		X			X					X		X		X	X	X
Total IgE	X		X			X					X		X		X	X	X
C-reactive protein	X		X			X					X		X		X	X	X
FeNO	X		X			X	X [n]	X [n]	X [n]	X [n]	X		X		X	X	X
Pulmonary Function Tests (Spirometry) [e]	X		X			X					X		X		X	X	X
Biomarkers [j]	X		X			X					X		X		X	X	X
Future analysis of additional cytokines	X		X			X					X		X		X	X	X
Flow cytometry [j]	X		X			X					X		X		X	X	X
CGI-C and ACQ-7 [h]			X		X						X		X		X	X	X
Serum samples for PK [i]	[redacted]																
Serum ADA and NAbs (immunogenicity)																	
Study drug administration	[redacted]																
Admission (Ad)/Discharge (Di)																	
COVID-19 protocol per site SOPs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
4-hour observation (post-dose)	[redacted]																
Subject contact [k]	(X)	(X)	(X)	(X)	(X)		(X)	(X)	(X)	(X)	(X)		(X)		(X)	(X)	(X)
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X		X		X	X	X
Assess injection site reactions	[redacted]																
Review/Record AEs	X	X	X	X	X	X	X	X	X	X	X		X		X	X	X

The legend and footnotes for Table 1 through Table 5 are listed below.

ACQ-7=Asthma Control Questionnaire; Ad=admission; ADA=anti-drug antibody; AE=adverse event; β-HCG=beta human chorionic gonadotrophin; BMI=body mass index; CGI-C=Clinician Global Impression of Change; COVID-19=Coronavirus disease 2019; D=day; Di=discharge; ECG=electrocardiogram; FeNO=fractional exhaled nitric oxide; FSH=follicle stimulating hormone; IFN λ=interferon gamma; IgE=immunoglobulin E; IL=interleukin; IP-10= interferon gamma-induced protein 10; NAbs=neutralizing antibodies; PK=pharmacokinetic; SOP=Standard Operating Procedures; TARC=thymus and activation-regulated chemokine; TB=tuberculosis; TSLP=thymic stromal lymphopoietin [redacted]=every [redacted] weeks; [redacted]=every [redacted] weeks; [redacted]=every [redacted] weeks; W=week.

[a] In women of childbearing potential at Visit 2 and at the Final Visit a serum β-HCG pregnancy test will be performed. At other visits a urinary pregnancy test will be performed. Follicle stimulating hormone will be assayed in women who on Visit 1 fit the post-menopausal criterion included in Section 4.8.4.

[b] A symptom-driven physical examination will be performed as needed based on reported signs and symptoms.

[c] Vital signs will be body temperature, pulse, respiratory rate, and blood pressure. See Table 9 for timing of assessments on dosing days.

[d] ECG assessments will be performed prior to any blood draws, FeNO measurements, and/or study drug administration. See Table 9 for timing of assessments on dosing days. All ECGs are performed in triplicate.

[e] Spirometry on Screening Visits 1 and 2 will be conducted at 60 minutes and 30 minutes prior to bronchodilator administration and at 30 minutes post-bronchodilator. At Visit 4 (Day 1) and at subsequent dosing visits, spirometry will be conducted approximately 60 minutes and 30 minutes prior to dosing (See Table 8). At non-dosing visits where spirometry is conducted, 2 assessments will be conducted 30 minutes apart; assessments should be conducted at approximately the same time as on dosing days. No post-bronchodilator spirometry will be performed.

[f] Blood samples will be collected for assessment of haematology including eosinophils. On dosing days, samples will be collected pre-dose. Coagulation studies will be performed only at Visit 1 and the Final Visit.

[g] On dosing visits, chemistry and urinalysis laboratory tests will be collected pre-dose.

[h] On days where Spirometry is not performed, ACQ-7 question 7 will be answered based on the FEV_1 value from the first measurement on the following morning

[i] Blood sampling for PK on dosing days will be collected pre-dose.

[j] Plasma levels of IL-5, IL-13, IFN λ, IL-17A, eotaxin-3, IP-10, and TSLP will be measured. Tryptase, carboxypeptidase, and TARC will also be measured.

[k] Subjects will be contacted by site personnel the day before each visit that includes a spirometric assessment to remind subjects of their visit and study rules. Subjects will also be contacted the day before their admission to the site.

[l] Flow cytometry samples will be collected and either analyzed or frozen. The decision to assay the frozen samples will be based on previous results.

[m] At Visit 5 (D2), Visit 6 (D4), Visit 16 (D86), Visit 17 (D88), Visit 18 (D92) and Visit 19 (D99) blood samples for haematology including eosinophils will only be collected for participants enrolled in Cohort 4.

[n] At Visit 5 (D2), Visit 6 (D4), Visit 16 (D86), Visit 17 (D88), Visit 18 (D92) and Visit 19 (D99) FeNO will be performed only for participants enrolled in Cohort 4.

6.4. Interim Analysis / Data Monitoring

An administrative interim analysis is planned for this study prior to the Primary Analysis. The results of the administrative interim analysis will have no impact on the trial design or analysis. A separate team will produce the results for this analysis and will have no further involvement in the study until after the study has been unblinded, see Section 10.1.3.

A Safety Review Committee will take place before the first subject in each of Cohorts 1 and 2 receive their third dose. All safety data available at that point will be reviewed by the SRC. The outputs that will be produced for the SRC and the remit of the SRC will be defined outside of the SAP as part of the SRC charter.

7. STUDY ENDPOINTS

7.1. Primary Endpoint

The primary endpoints are AEs, SAEs, physical examinations, clinical laboratory assessments, vital signs, and electrocardiograms (ECGs). Subject withdrawals, early terminations, and dosing compliance are also assessed. These endpoints are evaluated in the Safety Population.

7.2. Secondary Endpoints

The secondary endpoints include UPB-101 anti-drug antibodies (ADAs) and serum UPB-101 concentrations and analyses including C_{max}, t_{max}, AUC_{tau}. If appropriate, AUC_{inf}, $t_{1/2}$, apparent total body clearance after dosing (CL/F), and apparent volume of distribution during the terminal elimination phase after dosing (Vz/F), all after the first dose, will be analyzed as well. These endpoints are assessed from baseline through Week 24 in the PK Population.

7.3. Exploratory Endpoints

The exploratory endpoints include:

AEs, SAEs, pregnancy tests, and changes from baseline in physical examinations, clinical laboratory assessments, vital signs, and ECGs. Subject withdrawals, early termination, and dosing compliance are also assessed. Data collected from Baseline through Week 32 are included (data up to Week 24 are examined as part of the primary endpoints analysis). These endpoints are evaluated in the Safety Population.

UPB-101 ADAs, presence of neutralizing antibodies (Nabs) and serum UPB-101 concentrations and analyses including C_{max}, t_{max}, AUC_{tau}. Data collected from Baseline through Week 32 in the PK Population are included (data up to Week 24 are examined as part of the secondary endpoints analysis).

FeNO and blood eosinophil numbers from Baseline through Weeks 24 and 32. Total IgE; IL-5, IL-13, IL-17A, interferon gamma (IFN λ), IFN λ-induced protein 10 (IP-10), TSLP, eotaxin-3, tryptase, carboxypeptidase, thymus activation regulated chemokine (TARC), C-reactive protein (CRP) concentrations; and flow cytometric assessments of phosphorylated signal transducer and activator of transcription (pSTAT) and receptor occupancy will be evaluated from Baseline through Weeks 24 and 32. These PD markers are evaluated in the PD Population.

Clinician Global Impression of Change (CGI-C) and Subject Asthma Control Questionnaire (ACQ-7) from Baseline through Weeks 24 and 32. These PD markers are evaluated in the PD Population.

Forced expiratory volume in 1 second (FEV1) from Baseline through Weeks 24 and 32. These PD markers are evaluated in the PD Population.

8. SAMPLE SIZE

The primary objective of the study is to assess the safety and tolerability of UPB-101 when administered as multiple ascending doses. A sample size of 40 subjects with 8 subjects per cohort (6 on active drug + 2 on placebo) is considered sufficient to meet this goal. The sample size is not based on formal statistical hypothesis testing.

9. STUDY ANALYSIS SETS

The populations defined below will be reviewed against the study database at a BDRM at the time of the Final Analysis. The database at this time will be nearly final (i.e., the meeting may result in further data queries/changes post meeting), so inclusion/exclusion of subjects from study populations defined at this meeting will be further checked (post meeting) against a final locked database and will then be finalised prior to unblinding.

The following populations are defined:

Population	Description
Safety Population	Subjects who receive at least 1 injection of study drug
Pharmacokinetic (PK) Population	Subjects in the safety population who have a baseline result and at least one post-baseline PK result and for whom at least 1 PK parameter can be estimated.
Pharmacodynamic (PD) Population	Subjects in the safety population who have a baseline result and at least one post-baseline biomarker result.

The primary endpoint analysis will be based on the safety population as it will consist of safety and tolerability endpoints. The PK and PD populations will be used to analyse the PK, and PD endpoints, respectively.

In each population, subjects will be analyzed in the treatment group corresponding to the treatment (i.e., dose of active UPB-101 or placebo) they actually received.

10.PLANNED STATISTICAL METHODS

10.1. Statistical Considerations

10.1.1. General definitions

In all applicable summary/analysis presentations of safety endpoints, Baseline is defined as the last non-missing assessment value for a subject, for that particular parameter, that is prior to dosing with UPB-101 or placebo on Day 1 (including unscheduled assessments), unless over-ruled after review of data at the BDRM or otherwise stated in the appropriate endpoint sections below.

For efficacy endpoints, the baseline definition is as per the appropriate endpoint sections below. For the derivation of most efficacy endpoints, the first assessment to be used should be the first assessment that was taken after the first dose of study treatment.

A subject will be considered to have completed the study after his/her attendance at the last planned study visit (i.e., Week 32 visit), or the last unscheduled visit after the Week 32 visit (if any occur), as applicable.

Within summary presentations/analyses it is envisaged that only scheduled protocol visit values will be used for post-baseline time points. In the clinical database a number of data points have been labelled as unscheduled/additional recordings of data. These data points will be included within subject listings only. However, at the BDRM the occurrence of such unscheduled data will be reviewed for each subject to decide if (and how) any such data point(s) should be included within summary presentations/analyses. Any such decisions will be documented in the BDRM minutes.

10.1.2. Administrative Interim Analysis

An administrative interim analysis will be conducted prior to the Final analysis. This analysis is solely for internal decision-making pertaining to matters unrelated to the current study, UPB-CP-01, and so will have no bearing on the continued conduct and/or analysis of the study.

The administrative interim analysis will consist of a selected subset of the TFLs that will be produced for the final study reporting, identified in Section 13.

A separate unblinded team comprising of a statistician and programmers will produce the outputs for the administrative interim analysis. All data and outputs will be kept in a secure folder which is only accessible by the unblinded team for the administrative interim analysis. Since the Sponsor is unblinded, the results may be made available to all Sponsor personnel but not to any CRO or site personnel.

10.1.3. Data Presentation

The full list of TFLs to be produced for the final study analysis are shown in Section 13, and the specific format and content of each data Table/Listing presentation is shown in Section 14.

Summary Tables and Figures will be presented by treatment group (and also for an Overall column including all subjects, for selected data presentations). Within all Tables and Figures values for the treatment groups will be labelled as follows:

- [redacted] mg [redacted]
- [redacted] mg [redacted]

- [redacted] mg [redacted]
- [redacted] mg [redacted]
- Placebo and/or
- Screen Failures

An Overall column may be included in the disposition, and selected safety outputs which will include all treatment groups (Active and Placebo). Generally, the placebo groups will be pooled across all cohorts however, for some summaries placebo may be summarized according to dosing regimen (e.g. Placebo [redacted], Placebo [redacted]) or treatment group (e.g. Placebo [redacted]).

For screen failures, data is only expected in a selection of datasets. The data collected within these datasets will be included in the relevant listings only. Additional data that may have been collected for screen failures, in error, will not be displayed in the participants listings. They will not be included in any summary tables.

For selected outputs the dosing regimen may be used in the summaries where cohorts of the same dosing regimen (i.e. [redacted], [redacted]) will be grouped together, similarly cohorts may be grouped together by treatment group if there are multiple cohorts with the treatment group (e.g. [redacted]), or summaries may be produced combining all of the active groups together. The ordering of treatment groups shown here represents the order in which they will appear in outputs.

The scheduled protocol visits will be labelled in (applicable) report presentations as follows:

- Screening: Visit 1
- Screening: Visit 2
- Screening: Visit 3
- Day 1
- Day X (where X is the protocol specified Day, to be included within summary Table)
- Week X (where X is the protocol specified study Week, to be included within summary Table)

Generally, the summaries will be produced by Day, although in some cases it may be preferable to summarize by Week. This will be specified within each of the shells, as appropriate.

Note that the Baseline label will be used in some summaries, where Baseline will consist of data collected at the screening visits, on Day 1 pre-dosing or unscheduled assessments prior to dosing (if they are the last non-missing assessment). The actual Baseline definition will be provided in the section relevant for each endpoint.

Unscheduled visit data will be labelled as “Unscheduled” together with a date in data Listings. Unscheduled data will not be used in the summary tables unless otherwise agreed at the BDRM.

Where duplicate information is collected in both the database and in the vendor data transfer(s) (e.g., sampling date and time) this information will be reconciled by data management and then the information from the database will be included in subject Listings.

All variables will be listed to the same number of decimal places as reported. Descriptive statistics for all endpoints that are continuous data will have the following summary statistics presented in the following order: n, (arithmetic) mean (rounded to one more decimal place than recorded), geometric mean (for pre-specified endpoints only; rounded to one more decimal place than recorded), standard

deviation (rounded to two more decimal places than recorded), geometric standard deviation (for pre-specified endpoints only; rounded to two more decimal places than recorded), standard error (for pre-specified endpoints only; rounded to two more decimal places than recorded), median (rounded to one more decimal place than recorded), lower and upper quartiles (rounded to one more decimal place than recorded), minimum (as recorded), and maximum (as recorded).

Note: for endpoint(s) that require a geometric mean to be produced, and those endpoint(s) can have raw values of 0 (zero), the geometric mean calculation will add an appropriate constant value to all raw values prior to logging and will subtract that constant value from the final calculated anti-logged mean. The constant value used will be documented in the footnote of the tables. An example of such a calculation is shown below:

Geometric Mean = anti-log {mean (logged (base 10) endpoint values + 1)} - 1

Categorical variables will be summarized using proportions (counts and percentages). The specific approach to calculating percentages (relevant denominator) is detailed within each (relevant) Table template (Section 14).

Unless otherwise stated in the appropriate endpoint section(s) below, laboratory/efficacy parameter values that are below the level of quantification (BLQ), or less than the lower limit of quantification (<LLOQ) will be set to zero in computations for summary presentations and analysis but will be noted as below the limit of quantification in subject Listings.

10.1.4. Statistical Testing and Estimation

No formal statistical analysis will be performed within the SAP specified analysis.

10.1.5. Handling of Dropouts or Missing Data

In general, missing data will not be imputed and all summary statistics will be reported based upon observed data. For a limited number of summary presentations, missing data rules may be introduced. In particular, methods of handling incomplete dates for adverse events (Section 10.8.2) and incomplete dates for concomitant medications (Section 10.5) are presented. For any other data which has partial dates, which are required for use in time related calculations, these dates will be completed using a suitably conservative approach. Dates will be shown in subject Listings as they have been recorded.

10.1.6. Multiple Comparison/Multiplicity

As no formal hypothesis testing is taking place, no alpha adjustments will be made to handle multiplicity.

10.1.7. Examination of Subgroups

No subgroup analyses will be undertaken.

10.1.8. Model checking

As no formal hypothesis testing is taking place no formal model checking will be required.

10.1.9. Software

Data will be reported using SAS (version 9.4 or later).

10.1.10. Data Conversion (CDISC)

For the reporting of this study both CDISC SDTM (SDTM version 1.7 and SDTM Implementation Guide version 3.3) and ADaM (ADaM version 2.1 and ADaM Implementation Guide version 1.1) standards will be applied.

10.2. Participant Disposition

The number of subjects randomized, treated, received all doses as planned, received all doses expected, completed the Week 24 visit, and completed the study will be tabulated by treatment group, as well as the number who withdrew from the study and/or discontinue treatment early. The data on subject disposition and informed consent will be listed.

Note it was possible for participants to be rescreened. In order to maintain the link between screen failures and their subsequent rescreen records these will be displayed as XXXX/YYYY in all relevant listings (where screen failure data are displayed), where XXXX is the final screening number given to the subject and YYYY is the screening number under which the data being displayed was collected.

10.3. Protocol Deviations

Subject data will be reviewed for major protocol deviations by a qualified clinical reviewer prior to database lock and unblinding, at the BDRM at the time of the Final Analysis. All protocol deviations will be listed.

10.4. Demographic and other Baseline Characteristics

The Safety Population will be used in all presentations of demographic and baseline data. No statistical testing will be used to compare treatments for different baseline characteristics.

10.4.1. Demographics

Demographic variables at screening (sex, age, ethnicity, race, height (cm), weight (kg), and body mass index (BMI [g/m^2]), will be summarized by treatment group and across all subjects.

10.4.2. Other Baseline Characteristics

Smoking history, alcohol consumption and drugs of abuse information will all be listed

10.4.3. Medical History

All medical history will be coded using MedDRA, Version 25.0 (March 2022), summarized by treatment group and listed.

Asthma medical history will also be listed, as will allergy history and past and planned surgical procedures

10.5. Prior and Concomitant Medications

All medication terms will be coded using the World Health Organisation (WHO) Drug Dictionary Enhanced (WHO Drug Global, version March 1, 2022).

Background asthma medications are defined as medications taken for asthma at a stable dose during at least 3 months prior to randomization.

Other medications will be assigned as being prior to or concomitant with the treatment, based on the start and stop dates of the medication and the date of first dose of study treatment. If the medication stop date is before the date of first dose of study treatment, the medication will be assigned as being prior to study treatment. In all other situations, the medication will be assigned as being concomitant with study treatment.

Note: Start and Stop times will not be used for determining if a medication is concomitant or not.

All background asthma medications will be summarized, including the duration of exposure. Background asthma medications will also be listed, along with any changes from the stable dose that occur during the study.

All concomitant medications will be summarized by ATC class (Level 2) and preferred base name (WHO Code 01001). All medications will be listed.

10.6. Pregnancy

The results of pregnancy tests, both urine and serum, carried out throughout the study will be listed for all females. The results of the follicle stimulating hormone test will also be listed for the females who meet the post-menopausal criteria.

10.7. Other Baseline/Screening Tests

Drugs of abuse screening results will be listed, as will the results of any alcohol breath tests and urine cotinine tests.

10.8. Investigational Product Exposure

For each cohort the number and percentage of participants receiving each possible number of doses and injections will be tabulated. The details of each injection, including location and the reasons for incomplete and interrupted injections will be listed.

Planned Compliance will be calculated as: (the actual number of injections received / the number of injections planned given the assigned dosing regimen) * 100.

Expected Compliance will be calculated as: (the actual number of injections received / the expected number of injections given the assigned dosing regimen and the conduct of the trial) * 100.

The expected compliance accounts for the hold on dosing that occurred during the running of the trial during which subjects were not expected to have received any doses of study treatment, both will be listed.

10.9. Pharmacokinetic Analysis

The pharmacokinetic analysis will be reported separately, the specifications will be outlined within the PK analysis plan. This will include the identification of the PK population, the summary of the PK concentrations and PK parameters as well as the investigation of dose proportionality.

10.10. Immunogenicity Analysis

The immunogenicity analysis of neutralising antibodies and anti-drug antibodies will be reported separately, the specifications will be outlined within the PK analysis plan.

10.11. Pharmacodynamic Analysis

All Pharmacodynamic analysis will use the Pharmacodynamic population.

10.11.1. Biomarkers

The biomarkers collected in the study include cytokines (IL-5,IFN λ, IP-10, TSLP, eotaxin-3, TARC and lab parameters (Eosinophils, Total IgE and C-reactive protein). Receptor occupancy evaluated by flow cytometry, considered as a biomarker for target engagement, is also included.

All biomarkers, with the exception of the flow cytometry biomarker, will be summarized by visit as absolute values, change from baseline and percentage change from baseline, by treatment group. Any scheduled pre-baseline data will also be summarized by visit and treatment group.

Flow cytometry based evaluation of receptor occupancy (free receptors) will be calculated as the difference between the signal intensity (measured as % of TSLPR+ CD14+ cells) of the test sample and an aliquot of the same sample incubated ex vivo with saturating levels of UPB-101 prior to adding the detection antibody. The receptor occupancy will then be summarized at each visit, along with the percentage of free receptors, where;

% free receptors at any timepoint (t) = (difference between signal intensity at timepoint (t) / difference between signal intensity at baseline)* 100.

For negative % Free Receptors, set the value to 0. For % Free Receptors greater than 100%, set the value to 100%.

For all biomarkers the baseline will be the last non-missing result prior to first dose.

Any data that is below the limit of quantification will be replaced with zero before summarising but will be listed as '<BLQ'.

A mean plot of the biomarker results over time will be displayed, where the plots will display the mean at each visit +/- the standard error, with a line per treatment group.

10.11.2. Spirometry

FeNO and other spirometry parameters (FEV1, FEV1%, FVC and PEF) will be summarized by visit as absolute values, change from baseline and percentage change from baseline, by treatment group. Any scheduled pre-baseline data will also be summarized by visit and treatment group.

Plots of the mean over time will be displayed for each of the spirometry parameters listed above and all spirometry parameters collected will be included within subject listings.

Baseline for spirometry will be defined as the 60-minutepre-dose values at Visit 4. On all other dosing days the values recorded at 60 minutes pre-dose will be summarized. In case of multiple measurements at 60 minutes pre-dose (unexpected), the average of these will be used for baseline and the best (maximum) of these values will be used at the post-baseline timepoints. On all non-dosing post-baseline days the best (maximum) of the 2 measurements performed will be summarized.

10.11.3. CGI-C

The asthma clinician global impression of change (CGI-C) is a 7-point rating scale instrument used to assess the investigators evaluation of the change in asthma since baseline.

The rating scale uses the following categories:

1: Marked Improvement

2: Moderate Improvement

3: Minimal Improvement

4: No change

5: Minimal Worsening

6: Moderate Worsening

7: Marked Worsening

This assessment will be summarized as the number and proportion of subjects with each rating by treatment group at each visit this is collected.

A summary of the numerical score by treatment group and visit will also be displayed.

10.11.4. ACQ-7

The Asthma Control Questionnaire (ACQ-7) score is derived as an average of the responses to the 7 questions in the questionnaire. A subject is required to recall their asthma symptoms over the previous 7 days and respond, using a 7-point rating scale, to each question. The mean score is then categorised from 0 to 6, where 0 is totally controlled and 6 is severely uncontrolled.

This score will be summarized at each visit, by treatment group, along with the change from baseline in the mean ACQ-7 score.

10.12. Safety Analysis

The Primary endpoints for the study are safety related. All analyses of safety endpoints will be descriptive and will use the safety population. No statistical analysis of safety data will be performed.

10.12.1. Injection Site Reactions

For each injection site, information will be collected on whether any reactions are experienced by the subject. The number of subjects that ever experienced each of the reactions (pain, localised swelling, tenderness and erythema) will be summarized by treatment group, as well as the maximum severity experienced for each of the symptoms. Additionally, the number of subjects experiencing injection site reactions will be summarized by location and treatment group.

Erythema and swelling are recorded as size (in mm). The severity of these will be derived using the FDA guidance as below:

Erythema and Swelling Severity:

<2.5 cm = None
2.5 to 5 cm = Mild
5.1 to 10 cm = Moderate
>10cm = Severe.

The proportion of injections that resulted in reactions will also be summarized, by treatment group and all injection site reactions will be listed.

Any injection site reaction is also considered an adverse event of special interest and so the summaries of injection site reactions will be considered as part of the AESIs for the study.

10.12.2. Adverse Events

Adverse event (AE) data presentations will be produced for unsolicited adverse events that occur during the study.

All adverse events will be coded using MedDRA, Version 25.0.

Treatment emergent adverse events will be summarized over 2 distinct time periods within the study, from first dose of study treatment to Week 24, as well as from first dose of study treatment to Week 32 (i.e. over the entire study period).

Adverse events will be assigned to time periods according to the AE start and stop dates and times and dates/times of first dose of study treatment. Any adverse event with an onset date/time earlier than the date/time of first dose of study treatment will be classified as a pre-treatment adverse event. Any adverse event worsening in severity will be considered as a separate event, starting from the date/time of the updated severity.

Should any onset date for an adverse event be missing or only a partial date recorded (such that it cannot be determined if the event onset was prior to first dose of study treatment or not) then it will be assumed that the event is following first dose of study treatment, unless the adverse event stop date indicates otherwise.

If a subject experiences more than one adverse event with the same preferred term, that preferred term will be counted only once in summary presentations. It will be assigned the worst observed

severity and the strongest relationship to IMP among those events for the summaries in which those characteristics are considered.

Adverse Events of Special Interest (AESI) will be identified within the database as such. Additionally injection site reactions will be considered as AESIs.

An overall summary of adverse events will present the number of subjects with events and serious adverse events (also split by severity), number of subjects with adverse events and serious adverse events related to study treatment, the number of subjects with adverse events leading to discontinuation from study treatment or withdrawal from the study. This summary will be produced for adverse events occurring from first dose of study treatment to Week 24, and over the entire study period.

Additionally, each of the summaries below will be presented for the entire study period:

- Adverse Events by treatment group, System Organ Class (SOC) and Preferred Term (PT).
- Serious Adverse Events by treatment group, SOC and PT.
- Adverse Events by treatment group, SOC, PT and severity.
- Adverse Events related to study treatment by treatment group, SOC and PT.
- Adverse Events of Special Interest by treatment group, SOC and PT.

Listings will be provided for AEs, serious adverse events (SAEs), adverse events directly resulting in discontinuation of study treatment or withdrawal from study.

In all adverse event summary tables results will be displayed in descending order of the number of AEs across all active treatment groups by SOC and also preferred term within SOC.

10.12.3. Laboratory Variables

The following haematology, biochemistry, coagulation, viral serology and urinalysis parameters (as shown within the protocol) will be included within subject listings (and presented in the units as shown) and summary tables where relevant:

- Haematology: platelet count (x10^9/L), white blood cell (WBC) count (absolute) (x10^9/L), neutrophils (absolute) (x10^9/L), lymphocytes (absolute) (x10^9/L), monocytes (absolute) (x10^9/L), eosinophils (absolute) (x10^9/L), basophils (absolute) (x10^9/L), red blood cell (RBC) count (x10^12/L), haemoglobin (g/L).
    - Note: Complete blood count differentials are collected for this study but will only be listed and not included in any summaries, with the exception of the eosinophils differential which will be summarised as a biomarker (see Section 10.11.1).
- Biochemistry: sodium (mmol/L), potassium (mmol/L), glucose (mmol/L), albumin (g/L), chloride (mmol/L), bicarbonate (mmol/L), calcium (mmol/L), total protein (g/L), creatinine (umol/L), total bilirubin (umol/L), direct bilirubin (umol/L), phosphorus (mmol/L), alkaline phosphatase (ALP) (IU/L), alanine transaminase (ALT) (IU/L), aspartate transaminase (AST) (IU/L), urea (mmol/L), Total creatinine kinase (IU/L), HDL (mmol/L), Total Cholesterol (mmol/L), Triglycerides (mmol/L), C-reactive protein (mg/L).
- Coagulation: prothrombin time (PT) (secs), activated partial thromboplastin time (APTT) (secs), International normalised ratio.

- Other: HIV-1 and HIV-2 antibodies, hepatitis B surface antigen (HbsAg), hepatitis C antibodies (HCAb), FSH (IU/L), beta HCG (qualitative), QuantiFERON-TB Gold/Tuberculosis.
- Urinalysis: Specific gravity, pH, blood, protein, glucose, bilirubin, white blood cells, ketones, nitrites.
- Urinalysis (microscopy): Urine RBC (/HPF), Urine WBC (/HPF), Hyaline Casts, Cellular Casts, Granular Casts, Urine Culture.

Laboratory data collected in different units to that shown will be converted to the above specified units (if possible) for presentation in subject Listings.

Summary statistics for absolute and changes from baseline by timepoint, including pre-baseline timepoints, will be tabulated, by treatment group, for haematology, biochemistry and coagulation). Baseline here will be the last non-missing measurements taken prior to the first dose of study treatment. Shift tables will also be presented for the shift from baseline to above, below, or within normal range at each visit. Any scheduled pre-baseline data will also be summarized by visit and treatment group.

Categorical urinalysis parameter (not including microscopy, specific gravity or pH) will be summarized at each visit by the number and percentage of subjects having results in each category.

Laboratory parameters (Haematology, Biochemistry, Coagulation, Human Immunodeficiency Virus, Hepatitis A, B and C, Urinalysis and Urinalysis (microscopy) where done) will be included in subject listings. Laboratory values outside the normal range will be identified in subject listings as above or below the normal range.

Unscheduled visit assessments will be included within subject listings.

10.12.4. Vital Signs

Summary statistics for absolute and changes from baseline will be tabulated, by timepoint, including pre-baseline timepoints, and by treatment group, for vital signs parameters (systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg), pulse (beats/min), respiratory rate (RR) (breaths per minute), and temperature) and will be included within subject listings. Baseline vital signs are the last non-missing values taken prior to first dose of study treatment. Body measurements, height, weight and BMI will be listed separately.

10.12.5. Physical Examination

Physical examination findings will be listed, including the initial screening visit physical, the physical at Week 32 and any additional physicals carried out throughout the study. The listing will display the assessment (normal, abnormal not clinically significant, abnormal clinically significant) for each of the body systems assessed at each visit the physical examinations were performed.

10.12.6. 12-Lead ECG

ECGs will be carried out in triplicate at each visit and the mean of these three (or more) results will be used in any summaries.

Summary statistics for absolute values and change from baseline by time point, including pre-baseline timepoints, will be tabulated, by treatment group and for all subjects, for ECG parameters (Respiratory Rate (RR), Heart Rate (HR), Pulse Rate (PR), QRS duration (sec), QT interval (sec), QTcB interval (sec) and QTcF interval (sec)) and will also be included within subject listings, along with the overall

interpretation of the ECG. Baseline will be the last non-missing ECG results prior to the first dose of study treatment.

The shift in overall interpretation of the ECG from baseline, as defined by Clario, will also be presented at each scheduled visit.

Additionally, a table of the number and percentage of subjects with QTc in the ranges below will be presented by visit and treatment group: QTc interval > 450, QTc interval > 480, QTc interval > 500, QTc interval between 450 and 480 and QTc interval between 480 and 500 as well as change from baseline in QTc interval > 30, change from baseline in QTc interval > 60 and change from baseline between 30 and 60. The tables will display both QTcF and QTcB.

All ECG results will be listed, one for all Clario reported results, and another with the site interpretation as captured in the database.

11. CHANGES TO THE PROTOCOL SPECIFIED ANALYSIS DETAILED IN THE STATISTICAL ANALYSIS PLAN

The PK and PD Populations have been refined to clarify the need for baseline and post-baseline results for subjects to be included in either of these populations. The updates have been implemented to align the populations in terms of their requirement for post-baseline results.

It was initially planned to carry out analyses at 4 timepoints during the study: Part A – Week 24, Part A – Week 32, Part B – Week 24 and Part B – Week 32. It has since been agreed that only one formal analysis will take place, at Week 32, when all subjects (Part A and Part B) have completed the study.

During the study it was decided not to proceed with some of the exploratory cytokines. The cytokines that are available will be summarised as described in Section 10.11.1.

12.REFERENCES

13.TABLES, FIGURES AND LISTINGS

13.1. Specific Presentation Details

Tables, Listings and Figures will be provided in pdf and WORD format. All summary Tables and Figures will have source data footnotes that refer to the relevant Listings. Dates will appear as ddmmmyyyy and times as hh:mm (24-hour clock times). All Listings will be ordered by treatment group, subject number and scheduled visit. Any unscheduled visit information will also be included within the Listings, identified as unscheduled.

For the presentation of summary data, values will be aligned based on the unit column, and not left/right justified. For example:

Parameter		n	XX	XX
		Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)
		Median	XX.X	XX.X
	[optional]	GM (GSD)	XX.X	XX.X
		Q1, Q3	XX.X, XX.X	XX.X, XX.X
		Min, Max	XX, XX	XX, XX

All Tables, Listings and Figures will have the SAS program name, output filename and date of production in the footnote.

All Tables, Listings and Figures will include the following study header and footer:

CONFIDENTIAL Upstream Bio Page x of y
UPB-CP-01

Table X.X
Title
Population

Source Data: Listing 16.2.X {Source data footnote only appears for tables, where x references relevant listing number}

Program: XXXXXXXX Output: XXXXXXX Date: XXXXXXXXX

13.2. List of Tables

The columns Final and Admin Analysis identify the tables that will be produced for each of the Final Analysis and Administrative Interim Analysis, respectively.

Table Number	Table Title	Final	Admin Analysis
14.1.1	Subject Disposition – All Subjects	X	X
14.1.2	Demography and Baseline Characteristics – Safety Population	X	X
14.1.3	Medical History – Safety Population	X	
14.1.4.1	Concomitant Medications – Safety Population	X	
14.1.4.2	Background Asthma Medications – Safety Population	X	
14.1.5	Investigational Product Exposure – Safety Population	X	X
14.2.3.1.1	Biomarkers: Cytokines Change from Baseline Summary – Pharmacodynamic Population	X	X
14.2.3.1.2	Biomarkers: Cytokines Percentage Change from Baseline Summary – Pharmacodynamic Population	X	X
14.2.3.2.1.1	Biomarkers: Eosinophils Change from Baseline Summary – Pharmacodynamic Population	X	X
14.2.3.2.1.2	Biomarkers: Eosinophils Percentage Change from Baseline Summary – Pharmacodynamic Population	X	X
14.2.3.2.2.1	Biomarkers: Other Labs Change from Baseline Summary – Pharmacodynamic Population	X	X (IgE only)
14.2.3.2.2.2	Biomarkers: Other Labs Percentage Change from Baseline Summary – Pharmacodynamic Population	X	X (IgE only)
14.2.3.3.1	Biomarkers: Flow Cytometry Change from Baseline Summary – Pharmacodynamic Population	X	X
14.2.3.3.2	Biomarkers: Flow Cytometry Percentage of Baseline Summary – Pharmacodynamic Population	X	X
14.2.3.4.1.1	Biomarkers: FeNO Change from Baseline Summary – Pharmacodynamic Population	X	X
14.2.3.4.1.2	Biomarkers: FeNO Percentage Change from Baseline Summary – Pharmacodynamic Population	X	X

Table Number	Table Title	Final	Admin Analysis
14.2.3.4.2.1	Biomarkers: Other Spirometry Change from Baseline Summary – Pharmacodynamic Population	X	X (FEV1 only)
14.2.3.4.2.1	Biomarkers: Other Spirometry Percentage Change from Baseline Summary – Pharmacodynamic Population	X	X (FEV1 only)
14.2.4.1.1	CGI-C Summary – Safety Population	X	
14.2.4.1.2	CGI-C Categorical Summary – Safety Population	X	X
14.2.4.2.1	ACQ-7 Summary – Safety Population	X	X
	Safety		
14.3.1.1	Injection Site Reactions Summary – Safety Population	X	X
14.3.1.2	Injection Site Reactions by Location – Safety Population	X	
14.3.1.3	Injection Site Reactions - Proportion with Reactions – Safety Population	X	
14.3.2.1.1	Overall Summary of Treatment Emergent Adverse Events up to Week 24 – Safety Population	X	
14.3.2.1.2	Treatment Emergent Adverse Events by System Organ Class and Preferred Term up to Week 24 – Safety Population	X	
14.3.2.1.3	Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Severity up to Week 24 – Safety Population	X	
14.3.2.1.4	Treatment Emergent Adverse Events Related to IMP by System Organ Class and Preferred Term up to Week 24 – Safety Population	X	
14.3.2.1.5	Treatment Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term up to Week 24 – Safety Population	X	
14.3.2.1.6	Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term up to Week 24 – Safety Population	X	X
14.3.2.1.7	Treatment Emergent Adverse Events Leading to Discontinuation of Investigational Product by System Organ Class and Preferred Term up to Week 24 – Safety Population	X	

Table Number	Table Title	Final	Admin Analysis
14.3.2.1.8	Treatment Emergent Adverse Events Leading to Withdrawal from the Study by System Organ Class and Preferred Term up to Week 24 – Safety Population	X	X
14.3.2.2.1	Overall Summary of Treatment Emergent Adverse Events Over Entire Study Period – Safety Population	X	
14.3.2.2.2	Treatment Emergent Adverse Events by System Organ Class and Preferred Term Over Entire Study Period – Safety Population	X	
14.3.2.2.3	Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Severity Over Entire Study Period – Safety Population	X	
14.3.2.2.4	Treatment Emergent Adverse Events Related to IMP by System Organ Class and Preferred Term Over Entire Study Period – Safety Population	X	
14.3.2.2.5	Treatment Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term Over Entire Study Period – Safety Population	X	
14.3.2.2.6	Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term Over Entire Study Period – Safety Population	X	
14.3.3.1	Haematology Parameters Summary – Safety Population	X	
14.3.3.2	Haematology Parameters: Shift of Normal Range – Safety Population	X	
14.3.4.1	Biochemistry Parameters Summary – Safety Population	X	
14.3.4.2	Biochemistry Parameters: Shift of Normal Range – Safety Population	X	
14.3.5.1	Coagulation Parameters Summary – Safety Population	X	
14.3.5.2	Coagulation Parameters: Shift of Normal Range – Safety Population	X	
14.3.6	Urinalysis Parameters: Summary – Safety Population	X	
14.3.7	Vital Signs Parameters Summary – Safety Population	X	
14.3.8.1	Electrocardiogram Parameters Summary – Safety Population	X	

Table Number	Table Title	Final	Admin Analysis
14.3.8.2	Electrocardiogram Interpretation Shift Summary– Safety Population	X	
14.3.8.3	Electrocardiogram Category Summary – Safety Population	X	

13.3. List of Figures

The columns Final and Admin Analysis identify the figures that will be produced for each of the Final and Administrative Interim Analysis, respectively.

Figure Number	Figure Title	Final	Admin Analysis
14.2.1	Mean Plot of Biomarkers: Cytokines– Pharmacodynamic Population	X	X
14.2.2	Mean Plot of Biomarkers: Labs – Pharmacodynamic Population	X	X
14.2.3	Mean Plot of Biomarkers: Flow Cytometry – Pharmacodynamic Population	X	
14.2.4.1	Mean Plot of Biomarkers: Spirometry– Pharmacodynamic Population	X	X

13.4. List of Listings

The columns Final and Admin Analysis identify the tables that will be produced for each of the Final and Administrative Interim Analysis, respectively.

Listing Number	Listing Title	Final	Admin Analysis
16.2.1.1	Subject Disposition	X	X
16.2.1.2	Failed Inclusion and Exclusion Criteria for Screen Failures	X	
16.2.2	Protocol Deviations	X	X
16.2.3	Subject Populations	X	
16.2.4.1	Demographic and Baseline Characteristics	X	
16.2.4.2	Smoking History	X	
16.2.4.3	Alcohol Consumption History	X	
16.2.4.4	Reproductive Status and Contraception Use	X	
16.2.4.5.1	Medical and Surgery History	X	
16.2.4.5.2	Asthma Medical History	X	
16.2.4.5.3	Allergy History	X	
16.2.4.5.4	Past and Planned Surgical Procedures	X	
16.2.4.6.1	Prior Medications	X	
16.2.4.6.2	Concomitant Medications	X	
16.2.4.6.3	Asthma Medication	X	
16.2.5.1	Investigational Product Accountability	X	
16.2.5.2	Investigational Product Exposure	X	
16.2.6.1	Biomarkers: Cytokines	X	
16.2.6.2	Biomarkers: Labs	X	

Listing Number	Listing Title	Final	Admin Analysis
16.2.6.3	Biomarkers: Flow Cytometry	X	
16.2.6.4	Spirometry	X	
16.2.6.5.1	ACQ-7	X	
16.2.6.5.2	CGI-C	X	
16.2.7.1	Injection Site Reactions	X	
16.2.7.2	Adverse Events	X	X
16.2.8.1	Blood Sample Collection	X	
16.2.8.2.1	Haematology	X	
16.2.8.2.2	Chemistry	X	
16.2.8.2.3	Coagulation	X	
16.2.8.2.4	Urinalysis	X	
16.2.9.1	Other Laboratory Tests: Pregnancy	X	
16.2.9.2	Other Laboratory Tests: Drugs of Abuse Screen	X	
16.2.9.3	Other Laboratory Tests: Urine Cotinine	X	
16.2.9.4	Other Laboratory Tests: Alcohol Breath/Urine Test	X	
16.2.9.5	Other Laboratory Tests: Viral Serology	X	
16.2.9.6	Other Laboratory Tests: Other Tests	X	
16.2.10.1	Vital Signs	X	
16.2.10.2	Body Measurements	X	
16.2.11.1	Electrocardiogram – Clario	X	
16.2.11.2	Electrocardiogram - Site	X	
16.2.12	Physical Examination	X	

Listing Number	Listing Title	Final	Admin Analysis
16.2.13	Neurological Examination	X	
16.2.14	Visit Dates	X	

14.TABLE AND LISTING SHELLS