CLINICAL STUDY PROTOCOL: UPB-CP-01

Study Title: 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

Study Number: UPB-CP-01

Study Phase: Phase 1

Product Name: UPB-101

IND Number: Not Applicable

EudraCT Number: 2022-000132-36

Indication: Asthma

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	Version Number	Date
Original Protocol	Version 1.0	25 Feb 2022
Updated protocol	Version 2.0	28 March 2022
Updated protocol for submission	Version 3.0	01 April 2022
Update protocol following MHRA/REC review	Version 4.0	19 May 2022
Protocol Amendment 1	Version 5.0	18 August 2022
Protocol Amendment 2	Version 6.0	14 September 2022
Protocol Amendment 3	Version 7.0	27 October 2022
Protocol Amendment 4	Version 8.0	17 January 2023
Protocol Amendment 5	Version 9.0	31 March 2023

PROTOCOL SYNOPSIS

Sponsor: Upstream Bio

Intervention Name: UPB-101

Study Title: 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

Study Number: UPB-CP-01

Study Phase: Phase 1

Study Period: June 2022 – October 2023

Study Sites: 3-5 sites in the United Kingdom

Study Objectives and Endpoints:

Primary Objective	**Primary Endpoints**
To assess the safety and tolerability of UPB-101 when administered as multiple ascending doses.	• Adverse events (AEs), serious AEs (SAEs), physical examinations, clinical laboratory assessments, vital signs, and electrocardiograms (ECGs) from baseline through Week 24. • Subject withdrawals, early terminations, and dosing compliance from baseline through Week 24.
Secondary Objectives	**Secondary Endpoints**
To assess the immunogenicity of UPB-101 when administered as multiple ascending doses.	• UPB-101 anti-drug antibodies (ADA) from baseline through Week 24.
To characterize the pharmacokinetics (PK) of multiple ascending doses of UPB-101.	• Serum UPB-101 concentrations and analyses including maximum observed concentration (C_{max}), time to maximum observed concentration (t_{max}), area under the concentration-time curve under one dosing interval (AUC_{tau}) from baseline through Weeks 24. If appropriate, area under the concentration-time curve from the time of dosing extrapolated to time infinity (AUC_{inf}), terminal elimination half-life ($t_{1/2}$), apparent total body clearance after dosing (CL/F), and apparent volume of distribution during the terminal

	elimination phase after dosing (V_z/F), all after the first dose, will be analysed as well.
Exploratory Objectives	**Exploratory Endpoints**
To assess 32-week **extended** safety and tolerability of UPB-101 when administered as multiple ascending doses.	• AEs, SAEs, pregnancy tests, physical examinations, clinical laboratory assessments, vital signs, and ECGs from baseline through Week 32. • Subject withdrawals, early terminations, and dosing compliance from baseline through Week 32.
To assess 32-week **extended** immunogenicity of UPB-101 when administered as multiple ascending doses.	• UPB-101 ADAs from baseline through Week 32. • Neutralizing antibodies)NAbs) from baseline through Week 32.
To characterize 32-week **extended** PK of multiple ascending doses of UPB-101.	• Serum UPB-101 concentrations and analyses including C_{max}, t_{max}, AUC_{tau} from baseline through Week 32.
To assess the pharmacodynamic (PD) effect of UPB-101 on biomarkers related to asthma and/or the thymic stromal lymphopoietin (TSLP) pathway.	• Fractional exhaled nitric oxide (FeNO) and blood eosinophil numbers from baseline through Weeks 24 and 32. • Total immunoglobulin E (IgE), interleukins (IL)-5, IL-13, and 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), and flow cytometric assessment of phosphorylated signal transducer and activator of transcription (pSTAT) and receptor occupancy from baseline through Weeks 24 and 32.
To assess the PD effect of UPB-101 on clinician and subject impression of overall asthma severity.	• Clinician Global Impression of Change (CGI-C) from baseline through Weeks 24 and 32. • Subject Asthma Control Questionnaire-7 (ACQ-7) from baseline through Weeks 24 and 32.
To explore the PD effect of UPB-101 on lung function.	• Forced expiratory volume in 1 second (FEV_1) from baseline through Weeks 24 and 32.

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 up to 2 optional 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 3 to 5 cohorts: 3 cohorts in Part A and up to 2 optional cohorts in Part B. Eight subjects will be randomized per cohort (6 active, 2 placebo). A total of approximately 24 to 40 subjects will be enrolled in the study with 24 subjects in Part A and up to 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 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	[redacted]	[redacted]
	Placebo		
Cohort 2	UPB-101 [redacted] mg	[redacted]	[redacted]
	Placebo		
Cohort 3	UPB-101 [redacted] mg	[redacted]	[redacted]
	Placebo		
Description of SC Dosing Regimens in Part B (Adaptive Design)			
Cohort 4 (optional)	UPB-101 [redacted] mg	[redacted]	[redacted]
	Placebo		
Cohort 5 (optional)	UPB-101	• [redacted]	
	Placebo	[redacted]	

[redacted]

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 cohort 3 ([redacted] dosing intervals) will be observed for 5 months; subjects enrolled in cohort 4 ([redacted]) will be observed for 8 months.

All Study Periods: All PD and PK assessments (with the exception of spirometry) will be conducted between 6 AM and 10 AM to minimize the impact of diurnal variations on biomarker assessments.

Safety Review Committee

Part A

Subjects in Cohorts 1 and 2 will receive [redacted] doses of study drug. Before the first subject in each of those cohorts receives their [redacted] 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 [redacted] 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

If a [redacted] dosing regimen is selected for Cohorts 4 or Cohort 5 in Part B, an SRC meeting will be convened prior to the first subject in the relevant cohort(s) receiving their third dose. The data to be reviewed, and the process for the SRC to report their safety findings, will be as those detailed for Part A above.

Study Population

Approximately 24 to 40 subjects with mild-to-moderate asthma who meet the enrolment criteria will be enrolled/randomized in this study.

Inclusion Criteria:

1. Subject has signed, dated, and received a copy of the Independent Ethics Committee (IEC)-approved written ICF.
2. Subject is aged 18 to 60 years.
3. Subject has physician-diagnosed asthma.
4. Subject has a body mass index between 18 and 35 kg/m^2 at Visit 1.

5. Subject has either ≥200 eosinophils cells/µL **OR** FeNO >25 with ≥150 eosinophils cells/µL at Visit 1 or 2 AND ≥150 eosinophils cells/µL at the other visit.
6. Subject is:
   a. a female subject with reproductive potential who has a negative serum pregnancy test (beta human chorionic gonadotropin) during the Screening Period, is not breastfeeding, does not plan to become pregnant during the study, and agrees to use a highly effective birth control method when engaging in sexual activity with a male partner from the first dose of study drug until 120 days after the last dose of study drug or the Final Visit, whichever is later; **OR**
   b. a female subject either surgically sterile (i.e., post bilateral oophorectomy, hysterectomy, or tubal ligation) or naturally sterile (>12 consecutive months without menses with an elevated follicle stimulating hormone during the Screening Period); **OR**
   c. a male subject who is not sexually active; **OR**
   d. a male subject who is sexually active agrees to use a condom during the study from the first dose of study drug until 120 days after the last dose of study drug or the Final Visit, whichever is later.
   AND
   whose partner has childbearing potential must either be sterile (vasectomy with history of a negative sperm count at least 90 days following the procedure) or their partner must agree to use a highly effective birth control method from the first dose of study drug until 120 days after the last dose of study drug or the Final Visit, whichever is later.
7. Female or male subject agrees not to donate eggs or sperm, respectively, for a period of 120 days after the last dose of study drug.
8. Subject meets the Spirometry Performance Criteria:
   a. Pre-salbutamol/albuterol (hereafter referred to as salbutamol) FEV_1 ≥65% predicted normal value at Visit 1.
   b. Perform acceptable spirometry (i.e., meet American Thoracic Society/European Respiratory Society acceptability criteria) at Visits 1 and 2.
   c. Perform technically acceptable spirometry meeting repeatability criteria for FEV_1 during at least one (1) of the pre-bronchodilator assessments at Visits 1 and 2.
9. Medications:
   a. Subject is on stable, non-biologic asthma medication with no dose adjustments in the 8 weeks prior to Screening.
   b. Subject has not had an exacerbation of asthma (defined as an event requiring a change in asthma therapy) in the 8 weeks prior to Screening.
   c. Subject has not started any new prescribed drugs or had any dose adjustments in their prescribed drugs in the 8 weeks prior to Screening.

Exclusion Criteria:

1. Subject is an employee, consultant, and/or immediate family member (i.e., first degree relative, spouse, adoptee, or legal dependent) of the site or the Sponsor.

2. Subject is unreliable; incapable of adhering to the protocol and visit schedule according to the judgement of the Investigator; or has any disorder that may compromise their ability to give informed consent.
3. Subject has previous exposure to the study drug or known allergy/sensitivity to any of its excipients.
4. Female subject is pregnant or breastfeeding.
5. Subject cannot fast and avoid strenuous exercise for 9 hours prior to each site visit which includes clinical chemistry testing.
6. Subject has an abnormal medical history, physical finding or safety finding that in the opinion of the Investigator or Sponsor's blinded Medical Monitor may obscure the study data.
7. Subject has clinically significant history of a serious hypersensitivity reaction to any parenteral drug.
8. Any clinical laboratory test result outside of the reference ranges considered by the Investigator as clinically significant.
9. Subject has history or evidence of clinically significant pulmonary condition, including significant restrictive findings on pulmonary function testing, chronic bronchitis, emphysema, bronchiectasis, and pulmonary fibrosis, or any other related condition that in the opinion of the Investigator or Sponsor's blinded Medical Monitor may obscure the study data (e.g., gastro-oesophageal reflux and vocal cord paralysis/dysfunction).
10. Subject has donated blood (including blood products) or experienced loss of blood ≥500 mL within 8 weeks of Screening.
11. Screening supine blood pressure (BP) >150 mmHg (systolic) or >100 mmHg (diastolic), following at least 5 minutes of supine, semi supine or sitting rest. If BP is >150 mmHg (systolic) or >100 mmHg (diastolic), the BP should be repeated two more times and the average of the three BP values should be used to determine the subject's eligibility.
12. Subject has pacemaker; is not in sinus rhythm; has a resting heart rate <40 or >99 beats per minute; has a mean corrected QT interval (QTc; using Fridericia's [QTcF] formula) of >450 ms in males or >470 ms in females during the Screening Period; or has a left bundle branch block or bi-fascicular block.
13. Subject has a self-reported lower respiratory tract infection in the 8 weeks prior to Screening.
14. Subject has evidence of active or suspected bacterial, viral, fungal or parasitic infections within the past 8 weeks prior to Screening (e.g., sinusitis, common cold, viral syndrome, flu-like symptoms).
15. Subject has a history compatible with or diagnosis of a parasitic infection and has not been treated or has not responded to standard of care therapy.
16. Subject has Type I or II diabetes under poor glucose control.
17. Subject has an estimated glomerular filtration rate of <80 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration equation.

18. Subject has a history of malignancy of any type, other than *in situ* cervical cancer or surgically excised non-melanomatous skin cancers, within 5 years before Screening.
19. Subject has: (a) tested positive for illicit drugs, nicotine/cotinine, and/or alcohol at Screening; (b) consumed alcohol within 48 hours prior to Screening visits; and/or (c) refused to agree to consume <14 units per week (1 unit=½ pint beer, a 25 mL shot of 40% spirit or a 125 mL glass of wine).
20. Subject is positive for human immunodeficiency virus antibodies, hepatitis B surface antigen, or hepatitis C antibodies, or has a positive QuantiFERON®-tuberculosis Gold (QFT-G) test for tuberculosis at Screening. Subjects with an indeterminate QFT-G test may be re-tested; if a re-test remains indeterminant or is positive, the subject will be excluded.
21. Subject has received a vaccine dose within 28 days prior to Day -1.
22. Subject has received any immunosuppressant therapies including imatinib, ambrisentan, azathioprine, cyclophosphamide, bosentan, cyclosporine A, or methotrexate.
23. Subject has received an antibody or therapeutic biologic product during the 6 months prior to Screening.
24. Subject has received oral, intravenous, or intramuscular steroid within 8 weeks prior to Screening. Intrathecal or intra-articular steroids are permitted.
25. Subject has participated in a clinical study or has been treated with an investigational drug within 28 days or 5 half-lives, whichever is longer, prior to Screening.
26. Current tobacco smokers and those who have smoked within the last 12 months prior to Screening or prior to Day 1.
27. Subject has a positive COVID-19 test within 28 days of Day -1.

Test Product, Dose, and Mode of Administration:

Investigational materials are summarized below.

Product Description			
Product Name & Potency	**Dosing Strength**	**Dosage Form / Fill Count**	**Administration**
UPB-101 [redacted] mg/mL	[redacted] mg	[redacted] solution for injection	Delivered as [redacted] mL of the formulated solution per SC injection (containing [redacted] mg UPB-101)
UPB-101 [redacted] mg/mL	[redacted] mg	[redacted] solution for injection	Delivered as [redacted] mL of the formulated solution per SC injection (containing [redacted] mg UPB-101)
Placebo	[redacted] mg matching placebo	As supplied to site	Delivered as [redacted] mL of normal saline per SC injection.
Placebo	[redacted] mg matching Placebo	As supplied to site	Delivered as [redacted] mL of normal saline per SC injection.

SC=subcutaneous

Administration of the entire dose of study drug should not exceed 4 hours. Study drug may be administered in any extremity or in the abdominal wall. In exceptional cases where a subject cannot tolerate multiple SC injections, use of an infusion pump may be considered at the discretion of the Investigator.

Study Duration:

Approximately 9 months. All subjects will undergo Screening for a maximum of 3 weeks. Subjects assigned to a cohort with [redacted] doses administered [redacted] if such an interval is selected in Part B) will undergo 2 months of treatment followed by 6 months of observation. Subjects assigned to a [redacted] regimen will undergo 3 months of treatment followed by 5 months of observation. Subjects assigned to Cohort 4 will receive [redacted] dose followed by 8 months of observation.

Safety Assessments:

Safety and tolerability assessments will include AEs and SAEs, vital signs (BP, pulse, body temperature, and respiration rate), physical examinations, clinical laboratory parameters (haematology, clinical chemistry, coagulation, and urinalysis), ECGs, subject withdrawals, early terminations, and compliance.

Immunogenicity Assessments:

Serum samples will be collected for assessments of ADAs and Nabs. Samples from ADA-positive subjects will be tested using a NAb assay.

Pharmacokinetic Assessments:

Timed blood samples will be collected for serum. The PK analyses will be based on the timed blood PK sampling of all enrolled subjects (PK Population). Serum UPB-101 concentrations will be summarized using descriptive statistics. PK analyses will include maximum observed concentration (C_{max}), time to maximum observed concentration (t_{max}) and area under the concentration-time curve under one dosing interval (AUC_{tau}). A power model will be fitted using all doses and across all cohorts to assess dose proportionality for C_{max} and AUC_{tau} after the first dose. Within each dosing regimen, dose proportionality using a comparison of C_{max} and AUC_{tau} after the last dose will also be assessed using descriptive statistics. For each dosing regimen, accumulation of UPB-101 will be assessed by comparing the ratio of C_{max} and AUC_{tau} after the last dose and the first dose for each subject and summarized by dosing regimen.

Exploratory Assessments:

The PD effect of UPB-101 will be assessed by FeNO; blood eosinophil, total IgE concentrations, CRP, IL-5 and IL-13, IFN λ, IL-17A, IP-10, tryptase, carboxypeptidase, TARC, eotaxin-3, and TSLP levels; as well as flow cytometric assessment of pSTAT and receptor occupancy.

Additionally, a physician global impression of change will be assessed by the CGI-C questionnaire as well as by the ACQ-7 and pulmonary function testing will be conducted to assess FEV_1.

Statistical Methods:

Continuous variables will be summarized by UPB-101 dose group and pooled placebo, and by dosing frequency with descriptive statistics (e.g., number of observations, mean, standard deviation, median, interquartile range, maximum, and minimum). Categorical variables will be tabulated by frequency and percent of subjects per UPB-101 dose group and pooled placebo, and by dosing frequency. Demographic data will be summarized by treatment, dose, and dose regimen. Analyses will be based on observed data only; no data will be imputed.

Immunogenicity, PD biomarkers and clinical outcome measures such as FEV_1, CGI-C and ACQ-7 will be explored across dose cohorts using dose and exposure-response modelling to assess for dose and/or exposure related trends.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities and summarized by system organ class, preferred term, and treatment group for the number and percent of subjects reporting AEs, the number of events, and the number of subjects with any AE. All AEs will be listed including onset and resolution dates, verbatim term, preferred term, treatment, severity, relationship to treatment, action taken, and outcome. Absolute values and change from baseline laboratory evaluations, physical examinations, vital signs assessments, and ECG parameters will be summarized by visit and by treatment group. The frequency of subjects with safety laboratory results outside of normal reference ranges will be tabulated by treatment and visit. No inferential statistical analyses are planned for safety parameters.

Analysis of exploratory endpoints will be described in the Statistical Analysis Plan.

Sample Size Considerations:

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 24-40 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.

Version 9.0, 31 March 2023

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Ad	admission
ACQ	Subject Asthma Control Questionnaire
ACQ-7	Subject Asthma Control Questionnaire-7
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC_{inf}	area under the concentration-time curve from the time of dosing extrapolated to time infinity
AUC_{tau}	area under the concentration-time curve for one dosing interval
BMI	body mass index
BP	blood pressure
CGI-C	Clinician Global Impression of Change
CL/F	apparent total body clearance after dosing
C_{max}	maximum observed concentration
COVID-19	Coronavirus disease 2019
CPMP	Committee for Proprietary Medicinal Products
CRF	case report form
CRO	contract research organisation
CRP	C-reactive protein
D	day
Di	discharge
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
ERS	European Respiratory Society

EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FDA	Food and Drug Administration
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
β-HCG	beta human chorionic gonadotropin
HDL	high density lipoprotein
HED	human equivalent dose
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	identification
IEC	Independent Ethics Committee
IFN λ	interferon gamma
IgE	immunoglobulin E
IgG1	immunoglobulin G1
IL-	interleukin-
INR	International Normalized Ratio
IP-10	interferon gamma-induced protein 10
IV	intravenous
IXRS	interactive response system
LA-CRF	liver abnormality case report form
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
Mon	month
NAb	neutralizing antibodies
NOAEL	no observed adverse effect level

PD	pharmacodynamic
PIN	personal identification number
PK	pharmacokinetic
pSTAT	phosphorylated signal transducer and activator of transcription
PT	prothrombin time
PTT	partial thromboplastin time
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
QFT-G	QuantiFERON®-tuberculosis Gold
QTc	QT interval corrected
QTcF	QT interval corrected using Fridericia's formula
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOP	standard operating procedure
SRC	Safety Review Committee
$t_{1/2}$	terminal elimination half-life
TARC	thymus activation regulated chemokine
TB	tuberculosis
TBL	total bilirubin
TEAE	treatment-emergent adverse event
Th2	T helper 2
t_{max}	time to maximum observed concentration
TSLP	thymic stromal lymphopoietin
TSLPR	thymic stromal lymphopoietin receptor
ULN	upper limit of normal
US	United States

V_z/F	apparent volume of distribution during the terminal elimination phase after dosing
W	week
WBC	white blood cells
WMA	World Medical Association

TRADEMARK INFORMATION

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1 BACKGROUND AND RATIONALE

Upstream Bio intends that this clinical protocol and the performance of the study prescribed herein will comply with Good Clinical Practice (GCP), local, and national regulations governing this clinical study.

1.1 Indication

UPB-101 is a biologic under development for the treatment of subjects with asthma.

1.2 Asthma and TSLP

Thymic stromal lymphopoietin (TSLP) is an epithelial cell-derived cytokine that is produced in response to pro-inflammatory stimuli and drives allergic inflammatory responses primarily through its activity on dendritic (Reche, Soumelis et al. 2001, Soumelis, Reche et al. 2002, Gilliet, Soumelis et al. 2003) and mast cells (Allakhverdi, Comeau et al. 2009). The production of TSLP by the epithelium or mast cells is induced by stimuli such as allergen exposure, viral infection, cigarette smoke, etc (Takai 2012). Thymic stromal lymphopoietin signals through a heterodimeric receptor consisting of the interleukin (IL)-7 receptor alpha (IL-7Rα) chain and a common γ chain-like receptor (thymic stromal lymphopoietin receptor; TSLPR) (Pandey, Ozaki et al. 2000, Park, Martin et al. 2000). UPB-101 is a novel recombinant fully human immunoglobulin G1 (IgG1) monoclonal antibody targeting the TSLPR. Nonclinical pharmacology studies have demonstrated that UPB-101 binds to human and monkey TSLPRs and inhibits TSLPR-mediated signal transduction. Furthermore, UPB-101 has been observed to inhibit TSLP-stimulated myeloid dendritic cell-mediated differentiation of CD4+ T cells into mature T cells *in vitro*. In sensitized monkeys, UPB-101 suppressed ascaris extract-induced skin reactions, suggesting UPB-101 inhibits T helper 2 (Th2) type allergic responses.

Asthma is a chronic inflammatory disorder of the airways. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough. The aetiology of asthma is thought to be multi-factorial, influenced by both genetic and environmental mechanisms. The majority of cases arise due to hypersensitivity to allergens (atopy). Approximately 300 million people suffer from asthma worldwide, and it is anticipated that this number will increase considerably over the next 2 decades (Murdoch and Lloyd 2010). The prevalence of asthma in developed countries is >10% of the individual populations (Bousquet, Bousquet et al. 2005, Braman 2006).

Human TSLP expression is reported to be increased in asthmatic airways which correlates with disease severity; TSLP protein levels are detectable in the concentrated bronchoalveolar lavage fluid of subjects with asthma. A recent study demonstrated the association of a single nucleotide polymorphism in the human TSLP locus, 5.7 kB upstream of the transcriptional start site, with protection from asthma, atopic asthma and airway hyperresponsiveness. This suggested that differential regulation of expression of the TSLP gene might influence susceptibility to asthma (He, Hallstrand et al. 2009). Preclinical data additionally support a role of TSLP in asthma. These data suggest that targeting TSLP may serve to inhibit multiple

biological pathways involved in asthma, including but not limited to those involving IL-4 and IL-13.

Thymic stromal lymphopoietin is considered to play a critical role in asthma (Ying, O'Connor et al. 2005, Ying, O'Connor et al. 2008). Levels of both TSLP messenger ribonucleic acid and protein were increased in the airways of subjects with asthma, as compared with healthy subjects. Further, levels of TSLP messenger ribonucleic acid were increased in subjects with severe asthma despite the use of high doses of inhaled or oral corticosteroids (Shikotra, Choy et al. 2012). In transgenic mice engineered to express increased TSLP in the lungs, the airway inflammatory response was accompanied by an increase of immunoglobulin E (IgE) and pulmonary Th2 cytokine levels and airway hyperreactivity (Zhou, Comeau et al. 2005). Conversely, the suppression of Th2 cytokines and IgE production in the blood and the improvement of respiratory function have been observed in TSLPR-knockout mice and in asthma-model mice to which an anti-TSLPR antibody was administered (Al-Shami, Spolski et al. 2005, Zhou, Comeau et al. 2005, Shi, Leu et al. 2008). Further, several studies have shown a genetic association between a single-nucleotide polymorphism in the human TSLP gene locus and protection from asthma, atopic asthma and airway hyperresponsiveness, suggesting that differential regulation of TSLP expression might influence disease susceptibility (Hirota, Takahashi et al. 2011, Ferreira, Matheson et al. 2014, Eurostat).

Tezepelumab is a fully human monoclonal antibody that targets and blocks TSLP. In Phase 2 and Phase 3 clinical studies, long-term use of tezepelumab for up to 52 weeks significantly reduced rates of asthma exacerbations in subjects with uncontrolled asthma receiving standard of care treatment. This reduction was independent of baseline inflammatory biomarkers, including fractional exhaled nitric oxide (FeNO), blood eosinophil counts, and IgE, as well as being independent of allergic status (CPMP 1999, Corren, Parnes et al. 2017, Menzies-Gow, Corren et al. 2021). These results indicate that blocking TSLP activity is an effective treatment for subjects with asthma.

While tezepelumab binds to the TSLP ligand, UPB-101, a novel recombinant fully human IgG1 monoclonal antibody, targets the TSLPR. Nonclinical pharmacology studies have demonstrated that UPB-101, formerly referred to as ASP7266, binds to human and monkey TSLPRs and inhibits TSLPR-mediated signal transduction. Furthermore, UPB-101 has been observed to inhibit TSLP-stimulated myeloid dendritic cell-mediated differentiation of naive CD4+ T cells into mature T cells *in vitro*. In sensitized monkeys, UPB-101 suppressed ascaris extract-induced skin reactions, suggesting UPB-101 inhibits Th2 type allergic responses. In multiple preclinical *in vitro* and *in vivo* studies, UPB-101 demonstrated between 4-fold to 5-fold better potency relative to tezepelumab, when tested side-by-side in the same assays.

1.3 Unmet Medical Need

The prevalence of asthma in the general population ranges in the medical literature from 1 to 18% (Bousquet, Bousquet et al. 2005). Data from the European Union (EU) support a prevalence of 8.2% of the adult population and 9.4% of children (Eurostat 2021). Knowledge

of the pathophysiological mechanisms, genotypes, and phenotypes as well as therapeutic options has significantly increased dramatically since the 1980s. More recently, the introduction of biologic drugs for severe asthma has paved the way to a true revolution in the field of asthma management, by allowing a precision medicine approach to this chronic disease (Menzies-Gow, Corren et al. 2021).

Asthma affects an estimated 300 million individuals worldwide. It is a serious global health problem affecting all age groups, with increasing prevalence in many developing countries, rising treatment costs, and a rising burden for patients and the community. Asthma still imposes an unacceptable burden on health care systems, and on society through loss of productivity in the workplace and, especially for paediatric asthma, disruption to the family. Asthma still contributes to many deaths worldwide, including among young people (GINA 2021a).

Asthma management aims to achieve good control of symptoms, maintain normal activity levels, maintain lung function, and reduce the risk of flare-ups. Treatment generally involves inhaled corticosteroids, short-acting beta agonists, and long-acting beta agonists (GINA 2021b). Inhaled corticosteroids are the most commonly used asthma treatment while short-acting beta agonists are often used to treat mild intermittent asthma, and long-acting beta agonists and oral steroids are considered in more severe persistent asthma cases (Slater, Pavord et al. 2016, GINA 2021b).

In 2003, Xolair (omalizumab) became the first biologic licensed for asthma. As an inhibitor of IgE, Xolair targets subjects with allergic asthma. With some overlap in this subject population, IL-5 pathway inhibitors Nucala (mepolizumab), Cinqair (reslizumab), and Fasenra (benralizumab) target eosinophilic asthma. These products came to market relatively recently, gaining United States Food and Drug Administration (US FDA) approvals in 2015, 2016, and 2017, respectively. Dupixent (dupilumab) was approved in 2018 and is indicated to treat either subjects with an eosinophilic phenotype or those with oral corticosteroid-dependent asthma and targets Il-13 and IL-4. However, these products target severe asthma subjects and adoption is limited by high cost and payer access. Finally, the first TSLP inhibitor, Tezspire (tezepelumab) gained approval in Dec 2021 for subjects with severe asthma.

Despite the availability of several treatments that have been proven to be effective in most subjects, satisfactory asthma control remains an unmet need worldwide (Gruffydd-Jones 2019, WHO 2021). The burden of poorly controlled asthma is relevant in terms of both direct (e.g., health care services, medications) and indirect costs including work absenteeism, disability, and psycho-social costs. There is a need not only for more effective therapeutics but also for medications with better safety, tolerability, and compliance profiles (Caminati and Senna 2019). Drugs that treat all asthmatics irrespective of their phenotype (i.e., high or low eosinophil numbers) are particularly in demand.

Additional information can be found in the Investigator's Brochure (IB).

1.4 UPB-101 Clinical Summary

1.4.1 Completed Clinical Studies

One clinical study (7266-CL-0001) has been conducted with UPB-101, a first-in-human Phase 1a single-dose study in healthy volunteers under an FDA Investigational New Drug application.

Study 7266-CL-0001 was a randomized, subject- and Investigator-blinded, placebo-controlled, single ascending-dose (SAD) study to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of ASP7266 in healthy adult male and female subjects.

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.5 Study Rationale

The findings cited in Section 1.2 suggest that targeting TSLP signalling may lead to a treatment that could inhibit multiple biologic pathways involved in asthma. One clinical study with UPB-101 has been completed in healthy subjects (Study 7266-CL-0001). Overall, SADs of UPB-101 from [redacted] (i.e., [redacted] administered IV and SC were considered safe and well-tolerated in healthy male and female subjects.

The current study will assess the safety, tolerability, immunogenicity, PK, and PD of UPB-101 in multiple ascending doses administered SC in subjects with asthma. Results will inform the future clinical development of UPB-101.

1.6 Rationale of Study Design

The primary objective of this study is to evaluate the safety and tolerability of UPB-101 and thereby understand the clinical profile of UPB-101 to guide further clinical development as a treatment for asthma.

A placebo-controlled, double-blinded (Sponsor unblinded) design has been chosen to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of the results of this clinical study. Knowledge of treatment assignment could influence recruitment and allocation of subjects as well as safety and efficacy assessments. It is considered the optimal approach according to International Council for Harmonisation (ICH) E9 "Statistical principles in clinical studies" (ICH E9 1998).

Multiple dosing allows for assessment of UPB-101 at steady state, while the testing of ascending doses ([redacted] mg) along with the option to assess multiple dosing intervals will help establish the optimal dose and dosing frequency (based on safety, tolerability, immunogenicity, PK, and PD) to use in Phase 2 studies.

Safety, tolerability, immunogenicity, PK, and PD assessments will be conducted at specified intervals during the study keeping in mind $t_{1/2}$ and time to maximum observed concentration (t_{max}).

The use of placebo as control is considered the most reliable method to minimize subject and Investigator bias according to ICH E10 guidelines (ICH E10 2001) adopted by the Committee for Proprietary Medicinal Products (CPMP 1999) and the FDA. The use of placebo is recommended by the European Medicines Agency (EMA 2001) regulatory guidance in the design of dose-finding studies for moderate -to-severe asthma (EMA 2015) and this study will enrol only mild-to-moderate asthmatics. Additionally, during the study subjects are permitted to increase their asthma medication if their medical condition deteriorates.

1.7 Rationale of Dose Regimen and Duration of Treatment

In the non-clinical 26-week repeat dose toxicity study in cynomolgus monkeys, the no observed adverse effect level (NOAEL) was determined as [redacted] mg/kg for both male and female monkeys. The human equivalent dose (HED) for this NOAEL level is [redacted] mg/kg or a dose of [redacted] mg, assuming a 70 kg human (HED calculation according to guideline (FDA 2005)). The highest dose of [redacted] mg to be used in this study is [redacted]-fold lower than the HED NOAEL dose determined in non-clinical toxicity studies.

UPB-101 has been administered as a single IV dose from [redacted] mg to [redacted] mg ([redacted] mg/kg; assuming a 70 kg human) or a single SC dose of [redacted] mg ([redacted] mg/kg; assuming a 70 kg human) to healthy male and female subjects and is considered safe and well-tolerated (Study 7266-CL-0001). PK analysis found that area under the concentration-time curve from the time of dosing extrapolated to time infinity (AUC_{inf}) and C_{max} in that study increased dose proportionally. At the highest dose tested ([redacted] mg/kg), C_{max} and AUC_{inf} after a single IV administration were [redacted] µg/mL and [redacted] days·µg/mL, respectively. Bioavailability after SC administration was 70%. SC dosing was chosen for further development since this has significant benefits including potential self-administration.

PK modelling was performed based on the IV and SC data from Study 7266CL-0001. A two--compartment linear PK model was fitted to the mean data after single SC administration

of [redacted] mg/kg UPB-101 (Study 7266-CL-000). This PK model was subsequently used to predict exposure to UPB-101 after repeated SC administration at doses ranging from [redacted] mg and dosing intervals ranging from [redacted] to [redacted]. Predictions for repeated administration of UPB-101 assume that the PK is both dose- and time-independent.

Single Dose

Part A of the proposed study will explore SC doses in the [redacted] mg range. Table 1 lists the model-projected exposures following a single [redacted] mg SC injection in comparison to the maximal exposure that was found safe and well-tolerated in the SAD study (Study 7266-CL-000). The predicted maximal C_{max} and AUC_{inf} for a single injection in this study (at the highest dose of [redacted] mg SC) are [redacted]-fold and [redacted]-fold lower, respectively, when compared with the observed C_{max} and AUC_{inf} following administration of [redacted] mg/kg IV in Study 7266-CL-0001, a dose that was found to be safe and well-tolerated.

These data provide the rationale for the parallel cohort design. For all cohorts, the projected single dose exposures are lower than the exposures that were found to be safe and well tolerated in Study 7266-CL-0001.

Table 1 Predicted Mean PK parameters After Single SC Administration UPB-101 Compared to the Maximal IV Dose of Completed Study 7266-CL-0001

Route	Single Dose				Fraction of Maximal SAD Exposure	
	Dose (mg)	Dose (mg/kg)	C_{max} (µg/mL)	AUC_{inf} (days·µg/mL)	C_{max} IV/ C_{max} SC	AUC_{inf} IV/ AUC_{inf} SC
SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]	[redacted]		

AUC_{inf}=area under the concentration-time curve from the time of dosing extrapolated to time infinity; C_{max}=maximum observed concentration; IV=intravenous; PK=pharmacokinetic; SAD=single ascending dose; SC=subcutaneous.

Local Tolerability

All subjects enrolled in this study will receive [redacted] mg or [redacted] mg SC injections at each dosing visit depending upon to which cohort they are assigned. For example, subjects assigned to Cohort 1 ([redacted] mg [redacted]) will received two [redacted] mg SC injections at 2 separate injection sites at each dosing visit. The SC dose administered in the SAD study was [redacted] mg/kg ([redacted] mg) and was well-tolerated; no injection site reactions were reported. Therefore, no significant local skin reactions are anticipated in the current study.

Multiple Dose

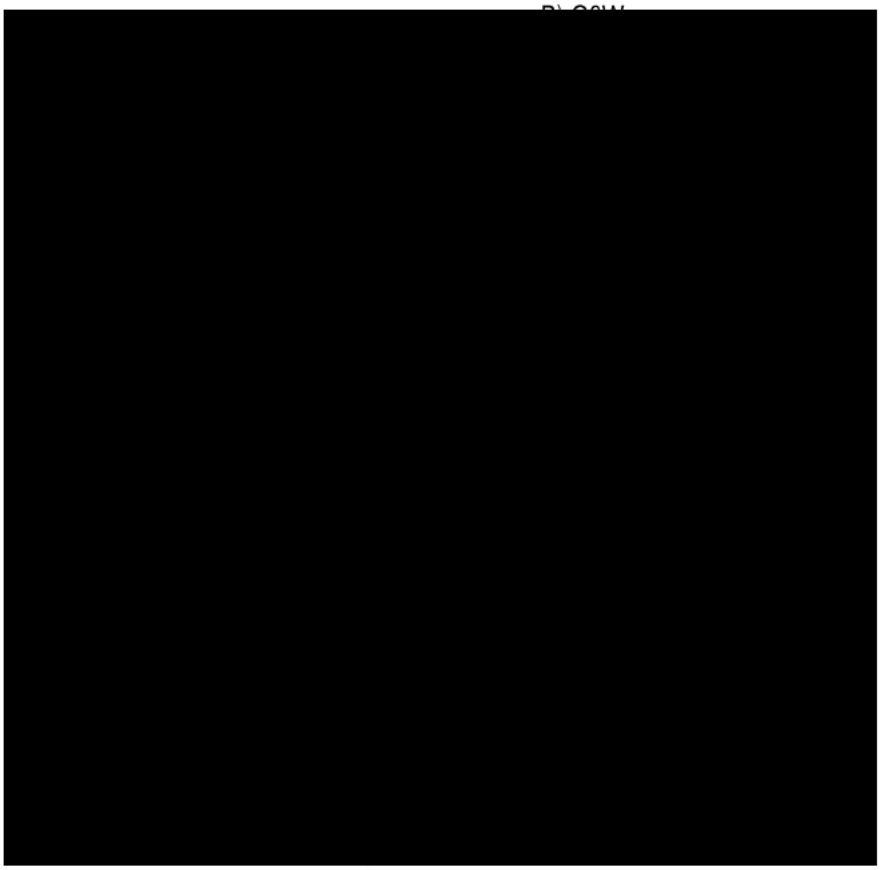
The PK model described above was used to simulate multiple dose PK for the doses and dosing intervals to be administered in this study. Predicted PK parameters and predicted mean PK profiles after repeated SC administration of UPB-101 are shown in Table 2 and Figure 1, respectively. There is minimal accumulation after repeated administration, with close to steady state levels reached after 3 injection (for [redacted] regimen) or 2 injections (for [redacted] and [redacted] regimens). The predicted C_{max} and area under the concentration-time curve for one dosing interval (AUC_{tau}) in this study (at the highest dose of [redacted] mg SC) are [redacted]-fold and [redacted]-fold lower, respectively, when compared with the observed C_{max} and AUC_{inf} following administration of [redacted] mg/kg IV in Study 7266-CL-0001, a dose that was found to be safe and well- tolerated.

Table 2 Predicted Serum PK Parameters After Repeated SC Administration of UPB-101

Dose	Frequency	Number of doses	Multiple SC dose		
			Interval	C_{max} (µg/mL)	AUC_{tau} (days·µg/mL)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AUC_{tau}=area under the concentration-time curve for one dosing interval; C_{max}=maximum observed concentration; D=day; PK=pharmacokinetic; [redacted]; [redacted]; [redacted]; SC=subcutaneous.

Figure 1 Simulation of Repeated Administration of UPB-101 Given as a SC Injection



[redacted]; SC=subcutaneous.

Based on the data from Study 7266-CL-0001 and the simulated data for repeated SC administration, the doses and dosing regimens selected for this study ensure that the minimum serum concentration remains above the estimated therapeutic target ([redacted] µg/mL) at nadir. This study will evaluate a representative range of doses and dosing regimens.

Maximal C_{max} Safety Margin

The NOAEL level in the non-clinical 26-week repeat dose toxicity study in cynomolgus monkeys was [redacted] mg/kg for both male and female monkeys. The C_{max} at NOAEL was [redacted] µg/mL, respectively for female and male monkeys. These levels are [redacted]-fold and [redacted]-fold higher than the highest projected C_{max} in this study, [redacted] µg/mL. Namely, these data provide a [redacted]-fold safety margin between the study's projected C_{max} and the observed non-clinical C_{max} at NOAEL in monkeys.

Study Posology

Part A will consist of 3 cohorts with fixed dosing regimens. Subjects in Cohort 1 will receive 3 doses of [redacted] mg study drug at a [redacted] dosing interval; Cohort 2 will receive 3 doses of [redacted] mg study drug [redacted]; Cohort 3 will receive 2 doses of [redacted] mg study drug [redacted]. The

PK and PD data obtained from Part A, including the long Observation Period following the final dose, will supply the Sponsor with information required for modelling doses and dosing intervals in preparation for Phase 2 development of UPB-101.

Part B, the optional adaptive design portion of the study, will afford the Sponsor an opportunity to fill any gaps in data that may remain following completion of Part A. For example, Part B will allow, as necessary, exploration of lower doses (e.g., [redacted] mg) and longer (e.g., [redacted] and/or [redacted]) dose intervals, as well as possible repetition of cohorts already concluded in Part A in order to enhance existing data. Subjects enrolled in Part B may receive doses [redacted] mg at dosing intervals of [redacted] x 3 doses, [redacted] x 2 doses, [redacted] x 2 doses, and/or [redacted] x 1 dose. Thus, the regimens selected for Part B will not exceed the exposures (i.e., doses and/or dosing intervals) included in Part A.

Since the Sponsor will be unblinded to the available safety, PK, and PD data accumulated during the study, the decision regarding doses and dosing intervals for subjects enrolled in Part B will be made while Part A is still ongoing. Therefore, Cohort 4 of Part B may begin without delay.

Each Dosing Period in Parts A and B is followed by an Observation Period to allow a full evaluation of safety, tolerability, immunogenicity, PK, PD, physician and subject global asthma status, and lung function.

The doses and dose regimens to be assessed in this study will inform the development of UPB-101 in Phase 2 and beyond.

1.8 Benefits and Risks Assessment

1.8.1 Patient Population

Asthma is characterized by a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness, cough that can fluctuate in intensity over time and variable limitations in expiratory airflow. In 2019, asthma affected approximately 262 million people worldwide.

1.8.2 Current Therapies

Five to 10% of patients with severe disease require high-dose inhaled corticosteroids and other medications to control their disease; others remain uncontrolled despite such therapies. In these patients, the inability to control their asthma, resulting in aggravated asthmatic symptoms, greatly reduces their quality of life, and increases healthcare costs.

1.8.3 Brief Summary of Product Data

UPB-101 (formerly referred to as ASP7266) is a novel recombinant fully human IgG1 monoclonal antibody targeting the TSLPR.

Non-clinical pharmacology studies have demonstrated that UPB-101 binds to human and monkey TSLPRs and inhibits TSLPR-mediated signal transduction. UPB-101 has been

observed to inhibit TSLP-stimulated myeloid dendritic cell-mediated differentiation of naive CD4+ T cells into mature T cells *in vitro*. In sensitized monkeys, UPB-101 suppressed ascaris extract-induced skin reactions, suggesting that UPB-101 inhibits Th2 type allergic responses.

The production of TSLP by the epithelium or mast cells is induced by stimuli such as allergens, bacteria, virus, chemical irritants, or physical trauma. TSLP is considered to be a "master switch" for allergy-induced inflammation. Targeting TSLP signalling may lead to a treatment that could inhibit multiple biologic pathways involved in asthma. Tezspire®, recently approved by the FDA for moderate-to-severe asthma, has a similar mechanism of action.

1.8.4 Study Rationale

This study will assess the safety, tolerability, immunogenicity, PK, and PD of UPB-101 in multiple ascending doses administered subcutaneously in subjects with asthma. Results will inform the future clinical development of UPB-101.

1.8.5 Rationale for Dose Selection for Proposed Study

In a non-clinical 26-week repeat dose toxicity study in cynomolgus monkeys, the NOAEL was determined as [redacted] mg/kg for both male and female monkeys. The HED for this NOAEL level is [redacted] mg/kg or a dose of [redacted] mg, assuming a 70 kg human (HED calculation according to guidelines guideline). The highest single dose of [redacted] mg that is to be used in this study is [redacted]-fold lower than the HED NOAEL dose determined in non-clinical toxicity studies.

1.8.6 Minimization of Risks in Study

Based on available non-clinical data, as well as known adverse effects of currently available biologic disease-modifying asthma agents, several potential risks have been identified for which mitigation actions have been developed to minimize the relevant risks in clinical studies of UPB-101. In addition, AE monitoring and other routine clinical and laboratory monitoring (including laboratory safety such as haematology and biochemistry, vital signs, physical examination, and ECGs) will be conducted.

To ensure subjects' safety, the protocol outlines the dose escalation process and dose stopping rules to be followed. Subjects will be followed for at least 12 weeks in consideration of the half-life of UPB-101 and to ensure adequate follow-up for immunogenicity monitoring. Subjects who have persistent anti-UPB-101 antibodies will continue to be evaluated until the level of these antibodies show evidence of declining, are no longer detectable, and/or are deemed to be of no clinical relevance. Based on the target organs of toxicity identified in the toxicology studies, the risk minimization actions that will be included in clinical studies are presented in Table 3.

Table 3 Risk Minimization Actions Based on Non-clinical Toxicology Studies

Target Organs	Theoretical/Potential Risks	Risk Minimization Action
Renal/Urinary System	Occult blood observed in urine of 1 animal at [redacted] mg/kg in the 4-week repeat dose toxicity study. Results were not reproduced in the 13- or 26-week repeat dose toxicity study at the same dose level.	Measurement of standard blood biochemistry and urinalysis during the Screening Period to exclude subjects with abnormal renal function and during the Dosing and Observation Periods to assure subject safety. Positive results from urinalysis will be confirmed with a microscopic examination.
Immunologic Response	Perivascular inflammatory cell infiltration in several organs as well as inflammatory cell infiltration in the alveoli and bronchioles associated with changes in blood chemistry including high globulin and γ-globulin ratio. Immune complex deposition in tissues was not demonstrable.	Standard safety monitoring and 12 weeks of immunogenicity follow-up.
Immunologic Response	Allergic reactions.	Close monitoring for 4 h after the injection including assessment of vital signs (body temperature, pulse, respiratory rate, and blood pressure). Medical personnel and resuscitation equipment immediately available on site.
Immunologic Response	Immune complex disease.	Assessments including medical history, physical examinations, and safety monitoring will be conducted.

1.8.7 Benefit/Risk Conclusion

This study is primarily a patient safety and tolerability study to inform further clinical development, and whilst those asthma patients who receive UPB-101 could derive benefit, this is not the main objective of the study. Subjects will continue to administer their usual stable, non-biologic asthma medication regimen during participation in the study.

The risks of participation are mainly those associated with possible side effects to UPB-101, although there may also be some discomfort from collection of blood samples and other study procedures. The study will be conducted at Medicines and Healthcare products Regulatory Agency (MHRA)-accredited Phase 1 facilities and procedures/interventions will be performed by qualified and trained professionals. Subjects will undergo Coronavirus disease 2019 (COVID-19) testing as per each site's protocol.

One previous human clinical study has been completed with UPB-101, in healthy volunteers, and in this study single increasing doses from [redacted] mg/kg body weight administered intravenously, or [redacted] mg/kg body weight administered subcutaneously, were considered safe

and well-tolerated. As detailed above, the Sponsor has identified risk minimization actions based upon non-clinical toxicology studies with UPB-101.

The Sponsor believes that the potential risks to subjects are proportionate for the proposed study, and that these will be addressed through risk minimization activities and through the conduct of the study at three sites with significant Phase 1 asthma clinical trial experience.

2 STUDY OBJECTIVES AND ENDPOINTS

Primary Objective

The primary objective in this study is the assessment of the safety and tolerability of UPB-101 when administered as multiple ascending doses.

Primary Endpoints

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. Data collected from baseline through Week 24 are included. These endpoints are evaluated in the Safety Population (defined in Section 9.3).

Secondary Objectives

The secondary objectives are the assessment of the immunogenicity and PK of multiple ascending doses of UPB-101.

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 (V_z/F), all after the first dose, will be analysed as well. These endpoints are assessed from baseline through Week 24 in the PK Population (defined in Section 9.3).

Exploratory Objectives

The exploratory objectives in this study include the assessments of the:

1. Extended 32-week safety and tolerability of UPB-101 when administered in multiple ascending doses.

2. Extended 32-week immunogenicity and PK of UPB-101 when administered in multiple ascending doses.

3. Pharmacodynamic effect of UPB-101 on biomarkers related to asthma and/or TSLP-related biomarkers.

4. Pharmacodynamic effect of UPB-101 on clinician and subject impressions of overall asthma activity.

5. Pharmacodynamic effect of UBP-101 on lung function

Exploratory Endpoints

The exploratory endpoints include:

1. 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. These endpoints are evaluated in the Safety Population (defined in Section 9.3).

2. 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 (defined in Section 9.3) are included.

3. 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 (defined in Section 9.3).

4. 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 (defined in Section 9.3).

5. Forced expiratory volume in 1 second (FEV_1) from baseline through Weeks 24 and 32. These PD markers are evaluated in the PD Population (defined in Section 9.3).

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a 2-part Phase 1, 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 SC to approximately 40 subjects with asthma. The study is expected to last from June 2022 to October 2023.

3.1.1 Study Design: Cohorts

The study will be conducted in 3-5 sites in the United Kingdom.

The study consists of Part A and Part B. Part A includes 3 cohorts with pre-set dosing regimens. Part B includes up to 2 optional 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 3 to 5 cohorts: 3 cohorts in Part A and up to 2 optional cohorts in Part B. Eight subjects will be randomized per cohort (6 active, 2 placebo). A total of approximately 24 to 40 subjects will be enrolled in the study with 24 subjects in Part A and up to 16 in Part B.

Part A

Subjects assigned to Part A will receive one of the following regimens:

Cohort 1 – 3 SC doses of [redacted] mg at [redacted],

Cohort 2 – 3 SC doses of [redacted] mg at [redacted], and

Cohort 3 – 2 SC doses of [redacted] mg at [redacted].

Part B

Part B will consist of up to 2 treatment cohorts. The dose and dosing intervals to be administered to subjects enrolled in these cohorts will be determined by the Sponsor based upon the available unblinded safety, PK, and PD data acquired in Part A. The decision regarding doses and dosing intervals for subjects enrolled in Part B will be made while Part A is still ongoing to allow Cohort 4 in Part B to begin without delay.

Safety Review Committee (SRC) meetings will be convened before administration of the third dose in Cohorts 1 and 2 and before the third dose in Cohorts 4 and/or 5 if a [redacted] regimen is selected for those cohorts. Details regarding the SRC and their responsibilities are provided in Section 5.8.

3.1.2 Study Design: Periods

The study will include 4 periods: Pre-screening, Screening, Dosing, and Observation.

Pre-screening

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 each subject considers consent for the full study. Pre-screening may occur within 90 days of Visit 1.

Screening Period

During the Screening Period (Day -21 to Day -1), subjects who have given written informed consent will be assigned a subject number, undergo Screening assessments which include, among other procedures, safety assessments. Eligible subjects will be allocated to cohorts and then be randomly allocated to treatment with UPB-101 or placebo in a 3:1 ratio, respectively.

On the afternoon before the first dosing (Day -1), subjects will be admitted to the site for review of their Day -5 assessments and final Screening procedures. Subjects who continue to meet the study enrolment criteria will continue to the Day 1 Visit.

Dosing Period

On Day 1, the first day of the Dosing Period, subjects will remain housed at the site and will undergo baseline safety, PD, PK and antigenicity assessments. Following completion of those procedures, subjects who remain eligible for enrolment will be randomized and administered the first dose of the study drug. Dosed subjects will remain at the site for a minimum of 4 hours post-dose to assure subject safety. Study drug will be administered SC as outlined in Table 12.

During the Dosing Period subjects will undergo frequent safety, PD, PK and antigenicity monitoring as well as study drug dosing according to the schedule listed in Table 4 through Table 9.

Subjects will be re-admitted to the sites the afternoon before each dosing to better assure attendance, study rule compliance, and adherence to the dosing day timelines. Several procedures will be performed upon admission. Food and exercise restrictions begin the evening after admission in advance of the assessments planned for the following day. The following morning between 6 AM and 10 AM, prior to dosing, subjects will undergo safety, PD, PK and antigenicity assessments. Once these procedures have been completed, subjects will receive their assigned study drug dose. Dosed subjects will remain at the site for a minimum of 4 hours post-dose to assure subject safety.

Observation Period

The Observation Period begins after each subject has received their final study drug administration. During this period subjects will undergo periodic safety, PD, PK and antigenicity monitoring according to the schedule listed in Table 6 through Table 8. Subjects enrolled in cohorts with [redacted] dosing intervals will be observed for 6 months while subjects enrolled in cohorts with [redacted] dosing intervals will be observed for 5 months. Subjects enrolled in cohort 4 (and receiving [redacted] dose) will be observed for 8 months.

Upon completion of the study, subjects will undergo a Final Visit. At that visit subjects will undergo final safety, PD, PK and antigenicity monitoring according to the schedule listed in Table 6 through Table 8. In addition to the usual safety assessments, all subjects will undergo a second complete physical examination and all females of childbearing potential will undergo beta human chorionic gonadotropin serum (β-HCG) pregnancy tests.

Subjects who withdraw their consent before they have completed all study visits and subjects who have completed all their planned study visits will be asked to attend their Final Visit at which time final safety and efficacy data will be collected.

All Study Periods

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

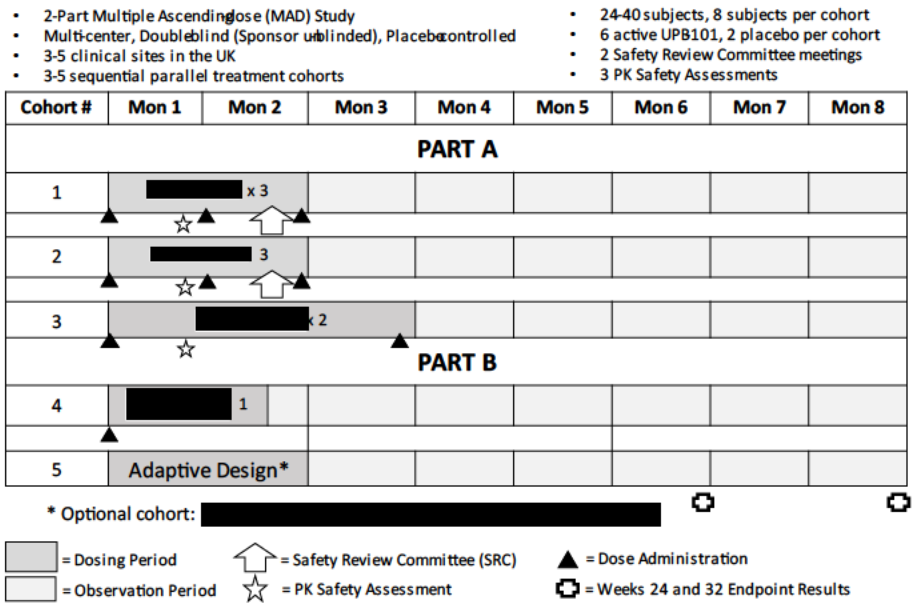
3.1.3 General Considerations for Study Conduct

Details of study drug dosing are provided in Section 7.2.

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.

The overall study design is presented in Figure 2.

Figure 2 Study Design



MAD=multiple ascending dose; Mon=month; PK=pharmacokinetics; [redacted]; UK=United Kingdom; #=number.

3.2 Study Activities

One day prior to visits that include a spirometric and/or clinical chemistry assessments, the site will contact the subject to remind them of the following study rules:

- To withhold all asthma medications the day of the study visit, or for at least 6 hours prior to start of study assessments.
- To fast (except for water) and refrain from vigorous exercise for at least 9 hours before a visit that includes a clinical chemistry assessment.
- Refrain from ingestion of leafy vegetables such as lettuce, spinach, kale and beetroot for 9 hours before visits.

At the start of each study visit, prior to any study procedures being performed, site personnel must confirm the subject withheld all asthma medications, including short-acting and -long-acting bronchodilators, for at least 6 hours before coming into the site, by confirming the last time of dosing for all asthma medication. Subjects who inadvertently took asthma medication within 6 hours of the start of study procedures must have their clinic visit delayed to later in the 6 AM to 10 AM window or rescheduled within the specified visit window.

The preferred order of assessments at all visits will be ECGs, vital signs, blood draws, FeNO, and lastly spirometry as appropriate for the study visit. Blood draws should ideally be performed in the morning to minimise diurnal variation in the level of eosinophils.

For all study visits, all PK and PD assessments (with the exception of spirometry) will be conducted between 6 AM and 10 AM to minimize the impact of diurnal variations on biomarker assessments. The site should make every effort to assess subjects at approximately the same time of day throughout the study and to dose subjects during the morning hours.

3.3 Schedule of Events

The Schedule of Screening Assessments for all cohorts is provided in Table 4. Assessments described in the Schedule of Events may be repeated during the study for safety reasons or if the assessment was deemed invalid (e.g., haemolysed blood sample).

Pre-screening

Sites may opt to utilize a pre-screening consent form to enable complete blood testing including eosinophil numbers, for consenting potential subjects, while they consider the ICF of the full study. Pre-screen may occur within 90 days of Screening Visit 1.

Screening Period (Visits 1, 2, and 3)

Screening Period consists of three visits. Prior to full execution of the ICF, no study-specific Screening procedures may be performed. However, once informed consent procedures have been completed, Visit 1 procedures may be initiated. Visit 1 will be performed no earlier than

21 days before Day 1. Procedures for Visit 1 may be conducted across multiple days if required, provided that the assessments are completed in advance of Visit 2.

Visit 2 will be performed at Day -5 to confirm the subject's eligibility; to perform eosinophil, PD, and safety assessments a second time; and to further acclimate the subjects to the Subject ACQ-7. Following review of the results of Visit 2 procedures, the site Principal Investigators will decide whom to advance to Visit 3.

Subjects will be admitted to the clinical research unit on Day -1 for final Screening assessments.

Table 4 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			Ad
COVID-19 protocol as per site SOPs	X	X	X
Subject contact	(X)	(X)	(X)
Review and record AEs	X	X	X

The legend and footnotes for this and all ensuing tables appear below.

Table 5 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	X					
UBP-101 administration/post-dose observation	X					
COVID-19 protocol as per site SOPs	X	X	X	X	X	X
Admission (Ad) or Discharge (Di) from site	Di					
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

Admission days are highlighted in light gray and dosing days in dark gray.

Table 6 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]		X			X	X	X	X	X	X	X	X	X	X	X	X
Serum ADA and NAbs (immunogenicity)		X			X						X	X		X		X
Study drug administration		[redacted]			[redacted]											
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]			[redacted]											
Admission (Ad)/Discharge (Di)	[redacted]	[redacted]		[redacted]	[redacted]											
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]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]								
Review/Record AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 7 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	±5	±5	±5	±5	±5
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 [j]	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 [i]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Serum ADA and NAbs (immunogenicity)	X			X						X	X		X		X
[redacted]				[redacted]											
COVID-19 protocol per site SOPs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]				[redacted]											
[redacted]			[redacted]	[redacted]											
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
Assess injection site reactions				[redacted]	[redacted]	[redacted]	[redacted]								
Review/Record AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 8 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]	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Serum ADA and NAbs (immunogenicity)	X					X		X			X				X		X
Study drug administration						[redacted]											
Admission (Ad)/Discharge (Di)					[redacted]	[redacted]											
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]	[redacted]	[redacted]	[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 4 through Table 8 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]; 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 analysed 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.

[o] For subjects enrolled in Cohort 4, Visit 15 (WK12) will be handled as a non-dosing visit. All Visit 15 (WK 12) assessments/activities will be performed as they would on a non-dosing visit. Activities directly related to dose administration and post-dose observation (admission, study drug administration, 4-hour observation, assessment of injection site reactions and discharge) will NOT be performed.

The timing of vital sign, ECG, and spirometric assessments on dosing days is presented in Table 9.

Table 9 Timed Assessments at Each Dosing Visit

	Pre-dose		Post-dose			
Clinical Variable	**-60 minutes (±15 minutes)**	**-30 minutes (±15 minutes)**	**30 minutes (±15 minutes)**	**1 hour (±15 minutes)**	**2 hours (±30 minutes)**	**4 hours (±30 minutes)**
Vital signs	X		X	X		X
Electrocardiogram	X				X	
Spirometry	X	X	X [a]			

[a] Spirometry will be obtained 30 minutes after the last injection is administered and may also be conducted at subsequent dosing visits if paradoxical bronchospasm is suspected.

3.4 Pre-Screening

Sites are encouraged to pre-screen subjects prior to consenting. Sites may opt to utilize a pre-screening consent form to enable complete blood testing including eosinophil numbers, for consenting potential subjects while they consider the ICF for the full study. Pre-screening may occur within 90 days before Screening Visit 1.

3.5 Screening Period

The goal of the Screening Period is to assess the eligibility of subjects, based on the criteria defined in Section 4. The assessments to be conducted on all cohorts during the Screening Period (Day -21 to Day -1) are found in Table 4.

Procedures to be performed during Visit 1, the first visit in the Screening Period, must not begin until completion of all informed consent procedures and the subject has received a fully executed copy of the ICF.

Subjects who continue to meet the enrolment criteria following review of all the results from Visit 1 will be invited to Visit 2. Visit 2 will take place on approximately Day -5 and is intended to assure that subjects deemed eligible after Visit 1 remain eligible and may be invited to continue to Visit 3 when limited safety assessments will be performed and subjects will be acclimated to the inpatient area.

3.6 Dosing Period

Subjects who complete Screening Visits 1 through 3 and continue to meet the study enrolment criteria may proceed to Day 1. Table 5 During the Dosing Period, enrolled subjects will receive study drug according to the cohort to which they are assigned and undergo safety, immunogenicity, PK and PD assessments.

3.6.1 Cohorts with [redacted] Dosing Intervals

The Dosing Period of cohorts with [redacted] dosing intervals (e.g., Cohorts 1 and 2 in Part A) will last [redacted] weeks (Days [redacted]). Subjects assigned to this cohort will receive 3 doses of study drug at [redacted] intervals. The assessments to be conducted on subjects in these cohorts during the Dosing Period and their timing are listed in Table 5 and Table 6.

3.6.2 Cohorts with [redacted] Dosing Intervals

While Part A does not include any cohorts with [redacted] dosing intervals, Part B might. The Dosing Period of cohorts with [redacted] dosing intervals will last [redacted] weeks (Days [redacted]). Subjects assigned to such a cohort will receive 2 doses of study drug, [redacted]-week apart. The assessments to be conducted on subjects in these cohorts during the Dosing Period and their timing are listed in Table 5 and Table 7.

3.6.3 Cohorts with [redacted] Dosing Intervals

The Dosing Period for cohorts with [redacted] (e.g., Cohort 3 in Part A) lasts [redacted] weeks (Days [redacted]). Subjects assigned to this cohort will receive 2 doses of study drug, [redacted] weeks apart. The assessments to be conducted on subjects in these cohorts during the Dosing Period and their timing are listed in Table 5 and Table 8.

The [redacted] cohorts may include either one or two dosing visits. In cohorts where only 1 dose is administered (such as cohort 4), the participants will undergo the same visits and procedures as those receiving 2 doses, but they will not be admitted to the unit on Day [redacted]. The assessments to be conducted on subjects in these cohorts during the Dosing Period and their timing are listed in Table 5 and Table 8.

3.7 Observation Period

Throughout the Observation Period, subjects will undergo safety, PD, PK, and immunogenicity assessments. No study drug will be administered during this period. Subjects assigned to cohorts receiving study drug [redacted] will be observed for 6 months. Subjects assigned to cohort 3 ([redacted] dosing intervals) will be observed for 5 months. Subjects assigned to cohort 4 ([redacted] dose) will be observed for 8 months.

3.7.1 Cohorts with [redacted] Dosing Intervals

The Observation Period assessments to be conducted in cohorts with [redacted] dosing intervals (e.g., Cohorts1 and 2 in Part A) and their timing are depicted in Table 6.

3.7.2 Cohorts with [redacted] Dosing Intervals

The Observation Period assessments to be conducted in cohorts with [redacted] dosing intervals and their timing are depicted in Table 7.

3.7.3 Cohorts with [redacted] Dosing Intervals

The Observation Period assessments to be conducted in cohorts with [redacted] dosing intervals (or receiving a single dose such as in cohort 4) and their timing are depicted in Table 8.

3.8 Unscheduled Visit and Early Termination Visit

Repeat assessments, if needed, will be captured as unscheduled visits if repeated on a separate day.

Early Termination Visits will be captured as unscheduled visits. The assessments conducted at the Early Termination Visit are the same as those conducted at the Final Visit of the Observation Period.

3.9 Procedures for Treatment Discontinuation and Study Withdrawal

Subjects who decide to discontinue study drug treatment or whose study drug is stopped by an Investigator will be encouraged to continue in the study as usual, including completion of the Observation Period, in order to collect full safety, PK, immunogenicity, and PD data. The date and reason for discontinuation of the study drug should be recorded in the electronic case report form (eCRF).

Subjects who received at least 1 dose of the study drug and withdraw at any point from the study completely should be asked to permit performance of an Early Termination Visit (see Section 3.8) in order to collect final safety, PK, immunogenicity and PD data. The date and reason for withdrawal from the study should be recorded in the eCRF. In addition, every effort should be made to obtain the subject's permission for collection of samples for PK and immunogenicity assessment 12 weeks after the last dose of study drug.

If a subject received all their expected study drug treatments but missed one or more Observation Period visits, the subject should resume study activities in the Observation Period based on the number of days that have elapsed following their last dose received. For example, if a subject is 14 days beyond their last dose, their next visit will be the first visit that occurs 14 days after their last dose.

If a subject withdraws from the study after randomisation but before receiving the first dose of study drug, then additional subjects may be enrolled to provide a sufficient number of subjects per cohort to address the study objectives (Section 4.10).

Subjects who contract COVID-19 after receiving the first dose of study drug should inform the study site and continue in the study as far as possible. When isolation or hospitalization is required and this coincides with a dosing visit, the Blinded Medical Monitor and the site Investigator will decide whether the dosing window should be extended or to stop future dosing.

3.10 Completion of Study

The Investigator will document the completion or the reason for a subject's early withdrawal from the study in the eCRF. The following categories should be used to describe these events in the eCRF:

- Subject discretion (document reason).
- Investigator considers it to be in the best interest of the subject.
- AEs.
- Administrative reasons (e.g., early termination of the study).
- Subject lost-to-follow-up.
- Major protocol deviation.
- Death.
- Completion of the study.
- Protocol-specified criteria (Section 4.9).

4 STUDY POPULATION SELECTION AND WITHDRAWAL CRITERIA

Approximately 24 to 40 subjects with mild-to-moderate asthma will be randomized. Each subject must meet the following criteria to be enrolled in this study.

4.1 Inclusion Criteria

1. Subject has signed, dated, and received a copy of the Independent Ethics Committee (IEC)-approved written ICF.
2. Subject is aged 18 to 60 years.
3. Subject has physician-diagnosed asthma.
4. Subject has a body mass index (BMI) between 18 and 35 kg/m^2 at Visit 1.
5. Subject has ≥200 eosinophils cells/µL **OR** FeNO >25 **with** ≥150 eosinophils cells/µL at Visit 1 or 2 AND ≥150 eosinophils cells/µL at the other visit.
6. Subject is:
   a. a female subject with reproductive potential who has a negative serum pregnancy test (β-HCG) during the Screening Period, is not breastfeeding, does not plan to become pregnant during the study, and agrees to use a highly effective birth control method when engaging in sexual activity with a male partner from the first dose of study drug until 120 days after the last dose of study drug or the Final Visit, whichever is later; **OR**
   b. a female subject either surgically sterile (i.e., post bilateral oophorectomy, hysterectomy, or tubal ligation) or naturally sterile (>12 consecutive months without menses with an elevated follicle stimulating hormone (FSH) during the Screening Period); **OR**
   c. a male subject who is not sexually active; **OR**
   d. a male subject who is sexually active agrees to use a condom during the study from the first dose of study drug until 120 days after the last dose of study drug or the Final Visit, whichever is later.
      AND
      whose partner has childbearing potential must either be sterile (vasectomy with history of a negative sperm count at least 90 days following the procedure) or their partner must agree to use a highly effective birth control method from the first dose of study drug until 120 days after the last dose of study drug or the Final Visit, whichever is later.
7. Female or male subject agrees not to donate eggs or sperm, respectively, for a period of 120 days after the last dose of study drug.
8. Subject meets the Spirometry Performance Criteria:
   a. Pre-salbutamol/albuterol (hereafter referred to as salbutamol) FEV_1 ≥65% predicted normal value at Visit 1.
   b. Perform acceptable spirometry (i.e., meet American Thoracic Society/European Respiratory Society acceptability criteria) at Visits 1 and 2.
   c. Perform technically acceptable spirometry meeting repeatability criteria for FEV_1 during at least one (1) of the pre-bronchodilator assessments at Visits 1 and 2.
9. Medications:

a. Subject is on stable, non-biologic asthma medication with no dose adjustments in the 8 weeks prior to Screening.
b. Subject has not had an exacerbation of asthma (defined as an event requiring a change in asthma therapy) in the 8 weeks prior to Screening.
c. Subject has not started any new prescribed drugs or had any dose adjustments in their prescribed drugs in the 8 weeks prior to Screening.

4.2 Exclusion Criteria

1. Subject is an employee, consultant, and/or immediate family member (i.e., first degree relative, spouse, adoptee, or legal dependent) of the site or the Sponsor.
2. Subject is unreliable; incapable of adhering to the protocol and visit schedule according to the judgement of the Investigator; or has any disorder that may compromise their ability to give informed consent.
3. Subject has previous exposure to the study drug or known allergy/sensitivity to any of its excipients.
4. Female subject is pregnant or breastfeeding.
5. Subject cannot fast and avoid strenuous exercise for 9 hours prior to each site visit which includes clinical chemistry testing.
6. Subject has an abnormal medical history, physical finding or safety finding that in the opinion of the Investigator or Sponsor's blinded Medical Monitor may obscure the study data.
7. Subject has clinically significant history of a serious hypersensitivity reaction to any parenteral drug.
8. Any clinical laboratory test result outside of the reference ranges considered by the Investigator as clinically significant.
9. Subject has history or evidence of clinically significant pulmonary condition, including significant restrictive findings on pulmonary function testing, chronic bronchitis, emphysema, bronchiectasis, and pulmonary fibrosis, or any other related condition that in the opinion of the Investigator or Sponsor's blinded Medical Monitor may obscure the study data (e.g., gastro-oesophageal reflux and vocal cord paralysis/dysfunction).
10. Subject has donated blood (including blood products) or experienced loss of blood ≥500 mL within 8 weeks of Screening.
11. Screening supine blood pressure (BP) >150 mmHg (systolic) or >100 mmHg (diastolic), following at least 5 minutes of supine, semi supine or sitting rest. If BP is >150 mmHg (systolic) or >100 mmHg (diastolic), the BP should be repeated two more times and the average of the three BP values should be used to determine the subject's eligibility.
12. Subject has pacemaker; is not in sinus rhythm; has a resting heart rate <40 or >99 beats per minute; has a mean corrected QT interval (QTc; using Fridericia's [QTcF] formula) of >450 ms in males or >470 ms in females during the Screening Period; or has a left bundle branch block or bi-fascicular block.
13. Subject has a self-reported lower respiratory tract infection in the 8 weeks prior to Screening.

14. Subject has evidence of active or suspected bacterial, viral, fungal or parasitic infections within the past 8 weeks prior to Screening (e.g., sinusitis, common cold, viral syndrome, flu-like symptoms).
15. Subject has a history compatible with or diagnosis of a parasitic infection and has not been treated or has not responded to standard of care therapy.
16. Subject has Type I or II diabetes under poor glucose control.
17. Subject has an estimated glomerular filtration rate of <80 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration equation.
18. Subject has a history of malignancy of any type, other than *in situ* cervical cancer or surgically excised non-melanomatous skin cancers, within 5 years before Screening.
19. Subject has: (a) tested positive for illicit drugs, nicotine/cotinine, and/or alcohol at Screening; (b) consumed alcohol within 48 hours prior to Screening visits; and/or (c) refused to agree to consume <14 units per week (1 unit=½ pint beer, a 25 mL shot of 40% spirit or a 125 mL glass of wine).
20. Subject is positive for human immunodeficiency virus antibodies, hepatitis B surface antigen, or hepatitis C antibodies, or has a positive QuantiFERON®-tuberculosis Gold (QFT-G) test for tuberculosis at Screening. Subjects with an indeterminate QFT-G test may be re-tested; if a re-test remains indeterminant or is positive, the subject will be excluded.
21. Subject has received a vaccine dose within 28 days prior to Day -1.
22. Subject has received any immunosuppressant therapies including imatinib, ambrisentan, azathioprine, cyclophosphamide, bosentan, cyclosporine A, or methotrexate.
23. Subject has received an antibody or therapeutic biologic product during the 6 months prior to Screening.
24. Subject has received oral, IV, or intramuscular steroid within 8 weeks prior to Screening. Intrathecal or intra-articular steroids are permitted.
25. Subject has participated in a clinical study or has been treated with an investigational drug within 28 days or 5 half-lives, whichever is longer, prior to Screening.
26. Current tobacco smokers and those who have smoked within the last 12 months prior to Screening or prior to Day 1.
27. Subject has a positive COVID-19 test within 28 days of Day -1.

4.3 Future Cohort Eligibility

Subjects who are declared screen failures due to eosinophil numbers will be ineligible for enrolment at any time during the study unless the eosinophil number which resulted in their ineligibility is considered to be low due to diurnal variations.

4.4 Re-screening Criteria

Subjects who following any Screening visit meet the enrolment criteria to proceed in the study but for some other reason (e.g., family emergency or coronavirus isolation) are not randomized may repeat the last visit performed provided Visit 3 will occur within the protocol-defined 21-day Screening Period.

Subjects who failed 1 or more criteria for reasons which in the opinion of the Investigator are likely to be remedied, may repeat the test(s) associated with those criteria (either at a subsequent Screening visit or at an unscheduled visit). In such situations the reasons for the repeat tests must be documented in the source notes and results which meet the criteria must be obtained prior to randomization.

However, subjects unable to complete screening within the protocol-defined Screening Period, must be declared a screening failure. Such Subjects may be re-screened from scratch.

4.5 Randomization Criteria

Subjects meeting all eligibility criteria (as defined in Section 4.1 and Section 4.2) at all three Screening visits are eligible for randomization on Day 1.

4.6 Subject Identification

All subjects who undergo Screening will be assigned a unique subject number at Visit 1. Randomization will be centralized using an interactive response system (IXRS).

4.7 Prior, Concomitant, and Prohibited Medications

All medications (prescription and over-the-counter), vitamin and/or mineral supplements, and herbal medicines or supplements taken at any time from Day 1 through the subject's last visit will be documented on the concomitant medication eCRF. Those taken within 8 weeks of Day -1 will be recorded as recent prior medication history. Information recorded will include start and stop dates and times, dose, frequency, route of administration, and indication (i.e., medical diagnosis and/or AE).

4.7.1 Allowed Medications to Treat Asthma

Subjects must be on a stable, non-biologic background asthma medication, including those used on an as-needed basis (e.g., single maintenance and reliever therapy), in the 8 weeks prior to Screening to be eligible for randomization. Background medications should remain stable for the duration of the study. However, background medication doses may be increased in response to worsening of asthma during the study.

Subjects <u>may not decrease</u> their prescribed asthma medications if they feel their asthma control has improved.

4.7.2 Prohibited Medications

No new concomitant medications (prescription or over-the-counter); no nutritional or dietary supplements, herbal preparations, or vitamins; and no concomitant procedures may be administered during the study, unless the Investigator (or designee) and/or Sponsor have given their prior consent. This prohibition does not apply to vaccinations. If new concomitant medications are initiated without the prior consent of the Investigator and Sponsor, the Investigator and Sponsor will review ongoing eligibility of the subject for the study.

4.8 Other Restrictions, Illicit Drugs, or Drugs of Abuse

4.8.1 Illicit Drugs

Illicit drugs or drugs of abuse, including methamphetamine and marijuana, will not be allowed from the start of Screening to the end of the Observation Period or Early Termination Visit. If any illicit drugs or drugs of abuse are used by the subject during the study, the dates of use and the amount will be documented, and the subject may be discontinued from study drug at the discretion of the Investigator. Subjects who are positive on drug Screening for a drug prescribed to that subject may be enrolled following approval by both the Principal Investigator and the Sponsor's blinded Medical Monitor.

4.8.2 Alcohol, Caffeine, and Tobacco Restrictions

Regular alcohol consumption will be limited in males and females <14 units per week (1 unit=½ pint beer, a 25 mL shot of 40% spirit or a 125 mL glass of wine). Subjects must refrain from alcohol consumption for the 48-hour periods prior to Screening and site visits.

The use of nicotine or tobacco containing products (including but not limited to snuff, chewing tobacco, cigars, cigarettes, pipes, vaping, or nicotine patches) will not be permitted for the duration of the study. Subjects will be tested for nicotine/cotinine during the Screening Period.

Subjects must refrain from caffeinated products (including caffeinated teas, coffees, cola and other beverages), chocolate-containing products, including drinks, and vigorous exercise for 9 hours before all study visits.

4.8.3 Dietary Restrictions

A diet rich in nitrate-containing food may increase FeNO (ATS 2005, Kerley, Kilbride et al. 2016, Kroll, Werchan et al. 2018). Therefore, subjects will avoid nitrate-rich foods, especially leafy vegetables such as lettuce, spinach, and kale, but also beetroot, for 9 hours before all study visits so as avoid complexity and potential errors.

Subjects will be fasting a minimum of 9 hours before visits that include clinical chemistry testing to afford accurate morning glucose and lipid testing.

4.8.4 Male and Female Contraception

Subjects must abstain from unprotected sex from the first dose of study drug until 120 days after the final dose of study drug or the Final Visit, whichever is later.

As per the Clinical Trial Facilitation Group guidance (CTFG 2020), female subjects of childbearing potential must use a highly effective method of birth control (i.e., failure rate <1% per year when used consistently and correctly) when engaging in sexual activity with a male partner from the first dose of study drug until 120 days after the final dose of study drug or the Final Visit, whichever is later. Highly effective methods of birth control are:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, implantable.
- Intrauterine device or intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized partner provided that the male partner is the sole sexual partner of the study participant, and that the vasectomized partner has received medical assessment of the surgical process.

Post-menopausal (naturally sterile) is defined as amenorrhea ≥1 year and a serum FSH concentration within the post-menopausal range.

Male subjects must use a condom with all partners through the study, from the time of the first dose of study drug until 120 days after the final dose of study drug or the Final Visit, whichever is later. Partners of male subjects who are not vasectomized and who are women of childbearing potential should use highly effective methods of birth control from the first dose of study drug until 120 days after the final dose of study drug or the Final Visit, whichever is later.

Subjects must refrain from gamete (i.e., sperm or egg) donation from the first dose of study drug until 120 days after the final dose of study drug.

4.9 Reasons for Treatment Discontinuation or Study Withdrawal

4.9.1 Duration of Study Participation

Subjects will remain in the study for approximately 9 months. All subjects will undergo Screening for a maximum of 3 weeks. Subjects assigned to a cohort with 3 doses administered [redacted] (or 2 doses [redacted] if such an interval is selected in Part B) will undergo 2 months of treatment followed by 6 months of observation. Subjects assigned to a 2-dose [redacted] regimen will undergo 3 months of treatment followed by 5 months of observation. Subjects assigned to a [redacted] regimen (ohort 4) will receive [redacted] dose followed by 8 months of observation.

A subject is considered to have completed study treatment if they completed the Dosing Period. A subject is considered to have completed the study if they completed the Dosing and the Observation Periods.

4.9.2 Reasons for Treatment Discontinuation

The subject may voluntarily discontinue study drug at any time without prejudice to further treatment.

Study drug treatment of individual subject may be discontinued at the discretion of the Investigator and/or the Sponsor due to clinically significant findings including but not limited to AEs, clinical laboratory abnormalities, or physical examination findings. See Section 5.9 for specific subject stopping rules. Subjects may also be discontinued from treatment for noncompliance, including starting a new concomitant medication (see Section 4.7.2).

If study drug is discontinued, the Investigator will report the discontinuation to the Sponsor's blinded Medical Monitor and document the date and reason for study drug discontinuation on the appropriate eCRF. Subjects who discontinue treatment will be encouraged to continue in the study and complete the remaining study visits, otherwise they will be asked to attend an Early Termination Visit (see Section 3.9). In addition, every effort should be made to obtain the subject's permission for collection of samples for PK and immunogenicity assessment 12 weeks after the last dose of study drug.

4.9.3 Reasons for Subject Withdrawal

Subjects may be withdrawn from the study at any time at their own request, upon request of the Investigator, or by Sponsor at any time or for any reason. A subject who withdraws consent will always be asked about the reasons and the presence of any AE.

Subjects will be withdrawn from the study by the Investigator and/or Sponsor for either of the following:

- If a female subject becomes pregnant during the study, the subject will be withdrawn from the study and the pregnancy will be followed through delivery or final outcome (see Section 8.9.8).
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.

A subject may also be withdrawn from the study by the Investigator and/or Sponsor at any time for other safety, behavioural, compliance, or administrative reasons such as the following:

- Significant noncompliance with study procedures/restrictions.
- If the subject no longer meets eligibility criteria.
- Study termination by the Sponsor.

Any subject who received at least one dose of the study drug and is about to be withdrawn from the study should be asked to undergo an Early Termination Visit (see Schedule of Events in Section 3.3) before subject withdrawal.

The Investigator must document the date and primary reason for the withdrawal on the appropriate eCRF. Subjects who withdraw prematurely may be replaced at the discretion of the Sponsor (see Section 4.10) to ensure adequate numbers of evaluable subjects.

4.10 Replacement of Subjects

Subjects who prematurely discontinue from the study before receipt of their first dose may be replaced as per Section 3.9. The IXRS will be programmed for the replacement subject to receive the same blinded treatment assignment as the subject who discontinued. The decision whether to replace the subject will be a joint decision between the Principal Investigator and the Sponsor.

4.11 Termination of the Study

An Investigator may choose to discontinue study participation at any time with sufficient notice by the Investigator for any reason as per the terms of the contract with the Sponsor.

The Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons. Such a termination must be implemented by the Investigator, if instructed to do so by the Sponsor, in a time frame that is compatible with the subjects' wellbeing.

4.12 Day 225 / Final Visit

The site visit on Day 225 is also referred to as the Final Visit in this document. This visit marks the last Observation Period visit.

5 STUDY SAFETY ASSESSMENTS AND PROCEDURES

The timing of study assessments and procedures for each part of the study is provided in the Schedule of Events in Section 3.3.

Assessments conducted during the Screening Period only are described in Section 3.5.

5.1 Medical History

Medical history, including any diseases, all past surgeries including skin procedures, and psychiatric illnesses will be documented.

Each subject will be questioned regarding any planned elective procedures that may occur during or following completion of the study, and these must be documented in the subject's medical record and the medical history section of the eCRF.

5.2 Prior Medication History

All medications or medical products taken by the subject within 8 weeks prior to Screening, whether the subject has stopped the medication or whether the subject has continued taking the medication, will be recorded as a Prior Medication History. This also includes medications taken as needed.

5.3 Demographics

The subject's gender, age, race, and ethnicity will be recorded.

5.4 Safety Assessments

Safety assessments will include AEs and SAEs, vital signs (BP, pulse, body temperature, and respiration rate), physical examinations, clinical laboratory parameters (haematology, clinical chemistry, coagulation, and urinalysis), ECGs, pregnancy tests, subject withdrawals, early terminations, and compliance.

5.4.1 Adverse Events

AE procedures are described in Section 8.

5.4.2 Vital Signs

Body temperature, pulse, respiratory rate, and BP will be collected. Assessments may be obtained while the subject is resting for 5 minutes in either the supine, semi-supine or seated position.

Heart rates are best obtained electronically, if available. If heart rate data are obtained electronically, the results may not be obtained from an ECG scheduled at the same time. If these data are obtained manually, a minimum observation period of 30 sec is required.

Respiratory rate will be determined following a minimum observation of 30 sec.

Assessment of vital signs will be conducted on visit days detailed in Table 4 to Table 9 in Section 3.3.

On dosing days, vital signs will be measured within 60 minutes pre-dose, 30-minutes, 1 hour, and 4 hours post-dose (see Table 9).

5.4.3 Weight, Height and Body Mass Index

Height for all subjects will only be collected at Screening Visit 1. Weight will be collected for each subject at Screening Visit 1 and at the Final/Early Termination Visit. BMI will be calculated at Screening Visit 1 to determine eligibility.

5.4.4 Physical Examination

The physical examination at Screening (Visit 1) and the Final/Early Termination Visit includes an assessment of general appearance, skin, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest (lungs), cardiovascular, abdominal, extremities, and musculoskeletal.

The Investigator will also be asked to assess whether the following neurologic functions are normal / abnormal.

- Mentation: appropriate behaviour; logical thought processes.
- Motor: use of all 4 extremities.
- Cerebellar: gait; balance standing and sitting.
- Cranial nerves: speech, facial symmetry, and hearing.
- A symptom-driven physical examination will be conducted in any other visits as needed based on reported signs and symptoms. If any physical examinations change from baseline, the Investigator will be asked to describe the new findings. Otherwise, except for at the time of the Final Visit, the physical examination will not have to be repeated.

5.4.5 Electrocardiogram

Electrocardiograms will be conducted on visit days detailed in Table 4 through Table 9 in Section 3.3. A standard 12-lead ECG will be recorded after the subject has been supine for at least 5 minutes. All ECGs will be acquired in triplicate with a maximum of 5 minutes between the first and the third recordings. All recordings will be transmitted to the central ECG laboratory for interval calculations and interpretation.

The Investigator or designated physician will review all ECGs and opine regarding the tracings. A paper printout of every ECG will be stored at the site.

All ECG will include at a minimum the subject's study number as well as the time and date of each recording. On dosing days, ECGs will be conducted within 60 minutes pre-dose and approximately 2 hours post-dose (see Table 9). ECG assessments will be performed prior to any scheduled blood tests, FeNO measurements, and/or study drug administration.

5.4.6 Clinical Laboratory Assessments

Clinical laboratory assessments include haematology, blood chemistry, and urinalysis as listed in Table 10. Subjects will have fasted (except for water) for a minimum of 9 hours prior to these assessments. On dosing days, samples will be collected pre-dose. All laboratory test results must be reviewed by the Investigator or qualified designee.

Table 10 Clinical Laboratory Tests[a]

Haematology	Chemistry	Urinalysis	Infectious Disease
Complete Blood Count	Sodium	Specific gravity	HIV
Automated differential[b]	Potassium	pH	Hepatitis B
PT, aPTT, and INR[c]	Chloride	Blood	Hepatitis C
	Bicarbonate	Protein	QuantiFERON®-TB Gold
	Urea	Glucose	
	Creatinine	Bilirubin	
	Total protein	WBC	
	Albumin	Ketones	
	Calcium	Nitrites	
	Phosphorus	Microscopic examination[d]	
	Glucose	Drug, nicotine, cotinine	**Miscellaneous**
	Total creatinine kinase		FSH[e]
	AST (SGOT)		Total IgE
	ALT (SGPT)		Pregnancy test (Section 5.4.7)
	Alkaline phosphatase		C-reactive protein
	Total bilirubin		Alcohol breath or urine test
	Direct bilirubin		
	HDL		
	Total cholesterol		
	Triglycerides		

ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase; FSH=follicle stimulating hormone, HDL=high density lipoprotein; HIV=human immunodeficiency virus; IgE=immunoglobulin E, INR=international normalized ratio, PT=prothrombin time, SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; TB=tuberculosis; WBC=white blood cell.

[a] Chemistry and urinalysis panels may be changed depending upon the clinical laboratory's standard panels.
[b] Eosinophil number from the complete blood count differential will be used for the eosinophil endpoint.
[c] Coagulation will only be performed at Visit 1 and at the Final visit.
[d] Microscopic examination will only be triggered if urine result is abnormal for blood, WBC, nitrites and/or protein.
[e] All females who are eligible based upon post-menopausal criteria as per Section 4.8.4.

Clinical laboratory assessments will be conducted on visit days detailed Table 4 through Table 9 in Section 3.3.

Results from the haematology test will be used to generate the eosinophil number. **Note: No eosinophil data collected after screening will be accessible to the site personnel (including the Investigators) to avoid unblinding them to the randomization assignment. To remove the possibility of eosinophil data being calculated from the remaining haematology parameters, data relating to monoctyes and basophils collected after screening will also not be provided to site personnel.**

5.4.7 Pregnancy Test and FSH

A β-HCG pregnancy test will be conducted for all female subjects with childbearing potential (as defined in Section 4.8.4) on visit days detailed Table 4 through Table 9 in Section 3.3. A urine pregnancy test will be performed at all visits noted in those tables except on Visit 2 and at the Final Visit when serum pregnancy tests will be performed. Subjects with a positive test result at any Screening visit will be ineligible for enrolment in the study.

In the event a female subject or the female partner of a male subject becomes pregnant during the study, the process described in Section 8.9.8 will be followed. Pregnant female subjects will be withdrawn immediately from the study (as described in Section 4.9.3) and followed as described in Section 8.9.8.

FSH will be assayed in women who on Visit 1 fit the post-menopausal criterion included in Section 4.8.4.

5.4.8 COVID-19 Testing

Subjects will undergo COVID-19 testing as per each site's protocol.

5.4.9 Subject Compliance Assessment

Subject compliance will be assessed by comparing the number of study drug doses the subject received to the number of doses the subject was scheduled to receive as per the protocol.

5.5 Immunogenicity Assessments

Serum samples for the assessment of UPB-101 ADAs and NAbs will be collected as detailed in Table 4 through Table 9 in Section 3.3.

Immunogenicity testing will follow a 3-tiered approach of screening, confirmation, and titration. Any sample screened as positive should be confirmed. Any confirmed positive sample should be titrated and tested for NAb activity and may be further characterized for quantity/titre, isotype, and affinity. Screening, confirmation, and titration assessments should be performed when samples are available; the NAb assay may be conducted later on frozen samples stored until needed.

5.6 Pharmacokinetic Assessments

Timed serum samples will be collected to determine the concentration of UPB-101 and will be collected as detailed in Table 4 through Table 9 in Section 3.3. Pharmacokinetic serum samples will be collected pre-dose on dosing days.

When the PK sampling coincides with the ECG and/or vital sign recordings, priority should be given to the ECGs and vital signs. The actual date and time of each PK sample collection will be recorded in the eCRF.

Blood sample collection, handling, and storage will be described in the laboratory manual.

The PK analyses will be based on the timed blood PK sampling of all enrolled subjects (PK Population). Serum UPB-101 concentrations will be summarized using descriptive statistics and used for PK analyses including the following endpoints if appropriate:

- C_{max}.
- t_{max}.
- AUC_{tau}.
- AUC_{inf} after the first dose, if appropriate.
- $t_{1/2}$, if appropriate.
- CL/F, if appropriate.
- V_z/F, if appropriate.

A power model will be fitted using all doses and across all cohorts to assess dose proportionality for C_{max} and AUC_{tau} after the first dose. Within each dosing regimen, dose proportionality using a comparison of C_{max} and AUC_{tau} after the last dose will also be assessed using descriptive statistics. For each dosing regimen, accumulation of UPB-101 will be assessed by comparing the ratio of C_{max} and AUC_{tau} after the last dose and the first dose for each subject and summarized by dosing regimen.

Analysis of UPB-101 will be performed using a validated method at a bioanalytical laboratory specified by the Sponsor.

5.7 Study Oversight

Primary oversight during the conduct of the study will be the responsibility of the Principal Investigators at each Study Site. The Principal Investigators are responsible for communicating any issues that may compromise subject safety to the Sponsor's blinded Medical Monitor.

5.8 Safety Review Committee

5.8.1 General Safety Monitoring

Results of the SAD study performed with UPB-101 were reported in Section 1.4.1. In that clinical study, UPB-101 was safe and well-tolerated. Since the highest dose administered in the completed single-dose Phase 1 was [redacted] mg/kg (the equivalent of approximately [redacted] mg), all 3 doses proposed for Cohort 1 ([redacted] and Cohort 2 ([redacted] as well as the 2 doses of Cohort 3 ([redacted]) in the current study are supported by those data. However, the SRC will meet before the first subject in any cohort with [redacted] dosing receives their third dose as an extra precaution so as to assure that formal reviews of all the available safety data occur at specific timepoints in the study.

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 SRC will be convened. The committee will review at each of the 3 meetings the safety data available at that point in time from all enrolling cohorts. Subjects enrolled in Cohort 3 will receive 2 doses of the study drug. Therefore, no SRC meetings will be directly linked to the progress of those cohorts. 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 (Section 5.9 and Section 4.11).

Part B: Study drug exposures in Cohorts 4 and 5 will not exceed the exposure of any of the cohorts in Part A. If a [redacted] dosing regimen is selected for Cohorts 4 or Cohort 5 an SRC meeting will be convened prior to the first subject in the relevant cohort(s) receiving their third dose. The data to be reviewed, and the process for the SRC to report their safety findings, will be as those detailed for Part A above.

The data will be blinded for review; however, if considered necessary, the SRC can request that data be unblinded for either individual subjects or the entire dose cohort. The randomization code will be broken following tranScrip's standard procedures.

The SRC will be comprised of individuals with expertise in internal medicine, clinical development, allergy and clinical immunology, clinical pharmacology, safety risk management, and clinical operations. The SRC will include Sponsor (Upstream Bio) personnel, the Principal Investigators (their designees), and external experts.

The SRC will consist of voting members (the chairperson and additional members) and non-voting members. Blinded voting members will be the following:

- Principal Investigators (or their designates) from each of the Study Sites.
- tranScrip's (the study clinical contract research organisation [CRO]) Head of Translational Medicine/Clinical Pharmacology.
- tranScrip's Clinical Development Team Lead – Chairperson.

The following non-voting members will support the SRC voting members in their role:

- Sponsor's unblinded Medical Monitor.
- tranScrip study statistician (blinded).

Other non-voting members may be added as needed to support the SRC.

All voting members will constitute a quorum. Any SRC recommendation will be made by a unanimous quorum vote at a meeting. Non-voting members cannot vote for cohort progression, study termination, or study enrolment halt. In an exceptional circumstance (e.g., illness or sudden unavailability), the Chairperson will have the discretion, in consultation with the SRC, to have a SRC recommendation made in the absence of a maximum of 1 voting member.

5.8.2 PK Safety Monitoring

When subjects enrolled in each cohort have completed their respective Day 22 procedures, serum PK samples collected following the first dosing will be assessed in a timely fashion for UPB-101 concentrations (PK). The PK results will be analysed, and a summary report will be written by the Sponsor's PK consultant with particular attention to C_{max} and AUC_{tau}, with a comparison to the pre-study PK modelling as described in Section 5.10. The report will be distributed to all members of the SRC. Unblinding individual subject PK data will not be included in this report so as not to unblind the blinded members of the SRC. After reviewing the summary safety, any member of the SRC may request a formal meeting of that committee to discuss the results.

5.9 Stopping Criteria

5.9.1 Study Stopping Criteria

If any of the following events develop during the study, at any dose of UPB-101, and these events are considered by the Investigator and/or Sponsor to be <u>at least probably related</u> to the administration of UPB-101, an *ad hoc* SRC meeting will be called <u>immediately</u> to investigate the event and to provide a recommendation for stopping or continuing the study or modifying the protocol:

- One or more subjects develop an SAE.
- Two or more subjects in the same cohort develop severe non-serious AEs, independent of within or not within the same system-organ-class.
- One or more subjects develop elevated plasma concentrations of ALT or AST ≥3-fold the ULN and elevated plasma concentrations of total bilirubin (TBL) ≥2-fold the ULN which is confirmed by repeat testing at least 48 to 72 hours after the initial test.

If the SRC recommends modifying the protocol as a condition for restarting the study, a protocol amendment will be submitted to the relevant regulatory authorities and IEC.

Procedures required prior to restarting a halted study are listed in Section 5.11.

Dose Escalation Stopping Criteria

If any of the following events develop during the study, dose escalation will be halted and the SRC will review the event and make a recommendation to stop dose escalation and/or continue dosing with modifications:

- Two or more subjects administered UPB-101 have an elevated plasma concentration of ALT or AST ≥3 × ULN that is considered by the Investigator and/or Sponsor related to the investigational product and is confirmed by repeat testing 48 to 72 hours after the initial test.
- Two or more subjects administered UPB-101 have an elevated plasma concentration of TBL ≥2 × ULN that is considered by the Investigator and/or Sponsor related to the investigational product and is confirmed by repeat testing 48 to 72 hours after the initial test.
- For additional information on hepatic parameter abnormalities, refer to Appendix 1, Liver Safety Monitoring and Assessment.
- One or more subjects administered UPB-101 has prolongation of QTcF, defined as QTcF >500 ms or >60 ms change from Baseline, that, on multiple ECGs, persists for at least 30 minutes and is considered by the Investigator and/or Sponsor related to the investigational product.
- Pharmacokinetic Stopping Rules – see Section 5.10.
- One or more subjects administered UPB-101 develop any other event that poses an unacceptable risk to other subjects in the study.

Procedures required prior to restarting a halted study are listed in Section 5.11.

5.10 Pharmacokinetic Stopping Limits

UPB-101 exposure at the NOAEL dose ([redacted] mg/kg IV) in the 26-week cynomolgus monkey study gave a C_{max} [redacted] µg/mL and AUC_{tau} [redacted] µg.day/mL, which are [redacted] **-fold** and [redacted] **-fold higher** than the predicted C_{max} and AUC_{tau} at the maximum dose ([redacted] mg SC) in the current study, which are [redacted] ug/mL and [redacted] day.ug/mL, respectively (see Section 1.7).

Despite the very large margins, if the following events develop during the study, the SRC will review the data and make a recommendation to stop dosing, continue dosing, or continue dosing with modifications: One or more subjects administered UPB-101 have C_{max} [redacted] of the preclinical NOAEL level, i.e., C_{max} [redacted] µg/mL.

Procedures required prior to restarting a halted study are listed in Section 5.11.

5.11 Re-starting the Clinical Study Following a Clinical Stop Due to a Stopping Rule

Should the clinical study be halted because of any stopping rule listed in Section 5.9 or 5.10 was triggered, the study restart will only be possible after receipt of written regulatory

authority approval via a substantial Clinical Trial Application amendment (with or without a protocol modification required by the SRC or Sponsor etc.).

6 STUDY EFFICACY ASSESSMENTS AND PROCEDURES

6.1 Pharmacodynamic Assessments

The assessments described in this section will be conducted to assess asthma-related PD biomarkers. Samples will be collected as indicated in Section 3.3; the actual date and time of each sample collection will be recorded in the eCRF. Blood sample collection, handling, and storage will be described in the specimen collection and processing instructions. Blood samples for biomarker analysis will be taken and frozen. The decision to assay the frozen samples will be based on results from earlier sample analyses.

On dosing days, all PD assessments must be completed prior to initiation of the study drug administration.

Numerous cytokines are involved in the pathogenesis of asthma and several additional biomarkers have been associated with asthma activity (Custovic, Siddiqui et al. 2022). Several approved or in development asthma medications target cytokines (Lambrecht, Hammad et al. 2019).

Plasma levels of IL-5, IL-13, IFN λ, IL-17A, eotaxin-3, IP-10 (C-X-C motif chemokine ligand 10), and TSLP will be measured using ultrasensitive assays. Tryptase, carboxypeptidase, and TARC will also be measured. CRP, and total IgE will be assayed by the central clinical laboratory.

Initially, select samples from those collected will be analysed and the resulting data assessed. Following this, should analysis of the remaining samples be deemed informative, they too will be analysed.

6.1.1 Fractional Exhaled Nitric Oxide

Measuring the FeNO level in asthmatic subjects is used as a surrogate marker for the presence and degree of airway inflammation. The FeNO levels will be measured via exhaled breath.

Subjects should refrain from eating nitrate-rich foods for at least 9 hours prior to FeNO measurements (see Section 4.8.3).

Assessment of FeNO will be conducted as detailed in Table 4 through Table 9 in Section 3.3.

6.1.2 Blood Eosinophils

Increased eosinophils are associated with increased severity, exacerbations, decreased lung function, and mortality in subjects with asthma (Hospers, Schouten et al. 2000, Garcia, Taille et al. 2013, Talini, Novelli et al. 2015, Price, Wilson et al. 2016). Blood eosinophils have become an established biomarker in inflammatory airway disease (Kostikas, Brindicci et al. 2018).

Absolute numbers of blood eosinophils will be measured using blood collected as part of the automated complete blood count clinical laboratory test which includes a differential count of white blood cells. Results will be reported at the highest precision (level of significant figures) offered by the clinical laboratory. Assessment of blood eosinophils will be conducted at the visits reflected in Section 3.3. The sites will be blinded to eosinophil count.

6.1.3 Total Immunoglobulin E

Total IgE is a well-established biomarker for severe asthma whose levels have been shown to be targeted and/or reduced by current biologic therapies (Lambrecht, Hammad et al. 2019). Total IgE levels will be measured as detailed in Table 4 through Table 9 in Section 3.3.

6.1.4 Flow Cytometry – pSTAT and Receptor Occupancy

Phosphorylated signal transducer and activator of transcription and receptor occupancy will be assayed via flow cytometry. Blood samples obtained from subjects will be analysed fresh or frozen. The decision to assay the frozen samples will be based on the results from the fresh samples. Analysis of blood samples (whether fresh or frozen) for pSTAT may be discontinued, based on assay status.

6.2 Asthma Status Questionnaires

6.2.1 Asthma Clinician Global Impression of Change

The CGI-C instrument is used to evaluate the overall response to treatment. The Investigator (clinician) will be asked to rate the degree to which the overall asthma status may have changed when compared to baseline (Day -1). It is recommended that the same clinician completes the CGI-C at all applicable visits for an individual subject.

Before making the assessment, the clinician will need to access and review the results from all relevant assessments, including pulmonary function tests performed before the visit. The assessment uses a 7-point rating scale: 1=Very Much Improved; 2=Much Improved; 3=Minimally Improved; 4=No Change; 5=Minimally Worse; 6=Much Worse; and 7=Very Much Worse.

Assessment of CGI-C will be conducted as detailed in Table 5 through Table 9 in Section 3.3.

6.2.2 Asthma Control Questionnaire

The Subject ACQ has 7 questions: the top scoring 5 symptoms, FEV_1% predicted, and daily rescue bronchodilator use. Subjects will be asked to recall how their asthma has been during the previous week and to respond to the symptom and bronchodilator use questions on a 7-point scale (0=no impairment; 6=maximum impairment). The Investigator will also score the FEV_1% predicted on a 7-point scale (0=no impairment; 6=maximum impairment). If the ACQ is completed on a visit where FEV_1% predicted is not measured, this question will be answered using the FEV_1% predicted from the first reading taken on the following morning.

The questions are equally weighted and the ACQ score is the mean of the questions and, consequently, ranges from 0 (totally controlled) to 6 (severely uncontrolled). The scale has been validated for use in both the clinical setting and in clinical studies.

The ACQ has strong measurement properties and has been fully validated for use in both clinical practice and clinical studies (Juniper, Bousquet et al. 2006). For clinical practice, clinical studies and epidemiological studies, the ACQ has strong discriminative and evaluative properties which means that it can detect small differences between subjects with different levels of asthma control and it is very sensitive to within-subject change in asthma control over time.

The ACQ can identify the adequacy of asthma control in individual subjects. In general, subjects with a score below 1.0 will have adequately controlled asthma and above 1.0 their asthma will not be well controlled. However, there is a very grey area between 0.75 and 1.25 where subjects are on the borderline of adequate control. On the 7-point scale of the ACQ, a change or difference in score of 0.5 is the smallest that can be considered clinically important.

Assessment of ACQ-7 will be conducted as detailed in Table 4 through Table 9 in Section 3.3.

6.3 Pulmonary Function Tests (Spirometry)

Spirometry will be conducted both to ensure no worsening of asthma during the study and as an exploratory PD endpoint. The spirometric exploratory analyses will be addressed in the Statistical Analysis Plan (SAP).

The site will be provided with a spirometry system with customized, study specific software. The volume accuracy of the spirometer across different flow ranges is to be checked with appropriate documentation via a printed calibration check report, prior to the conduct of spirometry on each test day. See Appendix 2 for spirometry performance criteria.

All study staff responsible for performing spirometry testing will receive training on the provide spirometry system and study specific software. All spirometry technicians are required to demonstrate proficiency in the use of the equipment and the ability to perform technically acceptable and repeatable spirometry sessions prior to performing testing on study subjects (see Appendix 2).

After completion of subject spirometry testing, the study staff will electronically transmit the spirometric measurements for centralized quality assurance review. Feedback on the quality of the spirometry data will be provided to the site and to the Sponsor or designee for central data management.

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 (after 4 puffs of salbutamol).

At Visit 4 (Day 1) and at subsequent dosing visits, spirometry will be conducted approximately 60 minutes and 30 minutes prior to dosing.

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 after Visit 2.

Subjects must withhold all asthma medications, including short-acting bronchodilators, for at least 6 hours before coming into the clinic on all scheduled spirometry visits. Subjects who inadvertently take asthma medication within 6 hours of the start of study procedures must have their clinic visit delayed (but not exceed study drug dosing by 10 AM) or rescheduled within the specified visit window.

Spirometry will be conducted as detailed in Table 4 through Table 9 in Section 3.3.

6.4 Future Analysis of Additional Cytokines

Additional blood samples will be collected as detailed in the Schedule of Events (Table 5 through Table 8 in Section 3.3) and the plasma stored for future analysis of asthma biomarkers not included in this study that would enhance the interpretation of the data generated. Examples of such biomarkers include cytokines (e.g., macrophage inhibitory proteins and IL-1β) and proteins (e.g., periostin) involved in inflammation, fibrosis, and/or re-modelling. No genetic testing will be performed on these samples.

6.5 Blood Sampling Volume per Subject

The total blood sampling volume for individual subjects in this study will not exceed 800 mL during the course of the study (32 weeks). The actual collection times of blood sampling may change, but the total blood volume collected will not increase. Additional blood samples may be taken for safety assessments at times specified by the Sponsor, provided the total volume taken during the study does not exceed 550 mL during any period of 90 consecutive days.

7 STUDY TREATMENT

7.1 Product Description

UPB-101 injection [redacted] mg/mL is a sterile, colourless to pale yellow, clear to slightly opalescent liquid solution supplied in a single-use vial with a coated rubber stopper and an aluminium cap. The description of UPB-101 and placebo are presented in Table 11.

Table 11 Product Descriptions

Product Description			
Product Name & Potency	**Dosing Strength**	**Dosage Form/ Fill Count**	**Administration**
UPB-101 [redacted] mg/mL	[redacted]mg	[redacted] solution for injection	Delivered as [redacted] mL of the formulated solution per SC injection (containing [redacted] mg UPB-101)
UPB-101 [redacted] mg/mL	[redacted]mg	[redacted] solution for injection	Delivered as [redacted] mL of the formulated solution per SC injection (containing [redacted] mg UPB-101)
Placebo	[redacted]mg matching Placebo	As supplied by site	Delivered as [redacted] mL of normal saline per SC injection.
Placebo	[redacted] mg matching Placebo	As supplied by site	Delivered as [redacted]mL of normal saline per SC injection.

SC=subcutaneous.

7.2 Treatment Administration

UPB-101 or matching placebo will be administered SC at the sites. All study drug dosing should be complete by 12 noon.

A description of the dosing regimens for the study is presented in Table 11 and described in further detail in Section 7.2.1.

Criteria for study drug discontinuation are provided in Section 4.9.1.

7.2.1 Dosing Instructions

Each vial is filled with an overfill sufficient to deliver [redacted] mL of the formulated solution (containing [redacted] mg UPB-101) or placebo.

Site personnel will administer [redacted] mL of formulated solution SC to deliver [redacted] mg of UPB-101, [redacted] mL to deliver [redacted] mg, or placebo per SC injection.

Table 12 Description of SC Dosing Regimens

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	[redacted]	[redacted]
	Placebo		
Cohort 2	UPB-101 [redacted] mg	[redacted]	[redacted]
	Placebo		
Cohort 3	UPB-101 [redacted] mg	[redacted]	[redacted]
	Placebo		
Description of SC Dosing Regimens in Part B (Adaptive Design)			
Cohort 4 (optional)	UPB-101 [redacted] mg	[redacted]	[redacted]
	Placebo		
Cohort 5 (optional)	UPB-101	• [redacted]	
	Placebo	[redacted]	

[redacted]; SC=subcutaneous.

In exceptional cases where a subject cannot tolerate multiple SC injections, use of an infusion pump may be considered at the discretion of the Investigator. Administration of the entire dose of study drug via an infusion pump should not exceed 4 hours.

7.2.2 Cohorts with [redacted] Dosing Intervals

In cohorts with [redacted] dosing intervals, the study drug will be administered on Days [redacted] for an [redacted]-week Dosing Period. Dosing will begin at [redacted] mg (Cohort 1). Once all 8 subjects have been enrolled in Cohort 1, Cohort 2 ([redacted] mg) will enrol the next 8 eligible subjects.

Prior to the administration of the third dose to subjects enrolled in Cohort 1, the SRC will meet as per Section 5.8. The same process will be repeated prior to the third dosing in Cohort 2.

7.2.3 Cohorts with [redacted] Dosing Intervals

In cohorts with [redacted] dosing intervals, study drug will be administered on Days [redacted] for an [redacted]-week Dosing Period.

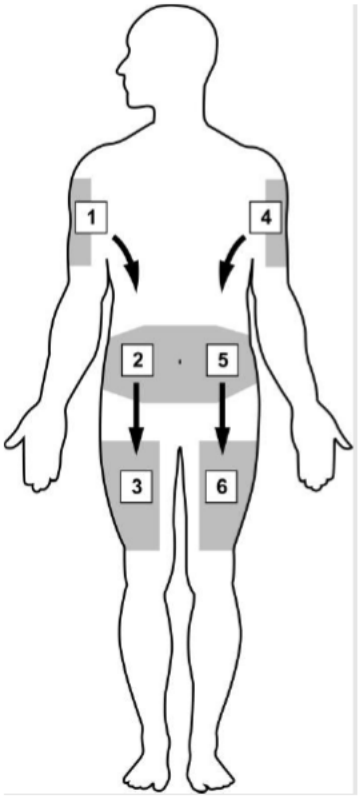
7.2.4 Cohorts with [redacted] Dosing Intervals

In cohorts with [redacted] dosing intervals, study drug will be administered on Days [redacted] for a [redacted]-week Dosing Period, except for Cohort 4 where study drug will be administered on Day 1 ONLY. None of the cohorts with [redacted] dosing are dependent upon the SRC recommendations.

7.2.5 Rotation of Injection Sites

Study drug may be administered in any extremity or in the abdominal wall. It is advised that the sites of injection be rotated, and the subject receive study drug injections in different anatomical sites at each administration. One suggested scheme of the injection site rotation is shown in Figure 3. For ease or tracking injection sites, suggested study drug administration locations for one study visit are: one injection in right upper arm, one injection in right abdomen, and one injection in right anterior thigh.

Figure 3 Rotation of Injection Sites



7.3 Preparation/Handling/Storage/Accountability

7.3.1 Acquisition and Accountability

The study drug will be packaged to support enrolment of the study. Qualified study personnel will have access to an IXRS to allocate subjects, to assign drug to subjects and to manage the distribution of clinical supplies. The study drug will be packaged according to a component schedule generated by the Sponsor. Each person accessing the IXRS must be assigned an individual unique personal identification number (PIN). They must use only their assigned PIN to access the system and they must not share their assigned PIN with anyone.

Under no circumstances will the Investigators allow the study drug to be used other than as directed by this protocol.

The study drug must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secure location to which only the Investigator and designated assistants have access. Storage conditions for the study drug should be observed, monitored, and documented. Study drug is to be dispensed only in accordance with this protocol. The Investigator or designee is responsible for keeping accurate records of the study received, the amount dispensed, and the amount remaining at the conclusion of the study. Study drug should be handled in accordance with Good Pharmacy Practices (i.e., gloves should always be worn by study personnel if directly handling any investigational medicinal drug). The Sponsor's blinded Medical Monitor should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, study drug should be accounted for and destroyed under local handling procedures and permission from the Sponsor.

Sites should discuss with the Sponsor representative for appropriate documentation that needs to be completed for drug accountability and destruction.

The Investigator or designated assistant should not open individual study drug until all pre-dose assessments have been completed and the subject has been approved by the Investigator to be randomized and enrolled into the study. Any deviation from this must be discussed with the Sponsor's blinded Medical Monitor.

All product complaints must be reported to the Sponsor. The Sponsor will contact the site to evaluate the nature of the complaint and determine what further action is needed, if applicable.

7.3.2 Primary Packaging and Labelling Information

Investigational materials will be packaged by the Sponsor.

Labels will be printed with black ink and may include the following text:

Lot # (Packaging Lot Trace ID) Kit # Expiration date Subject # Investigator Space for subject # Contents Visit # Product identifiers (name and strength)	Storage conditions Protocol # Country regulatory requirements Sponsor name, address, and telephone number Route of administration Directions for use Caution statement (to be used by qualified Investigators only)

ID=identification; #=number

Each vial will be labelled with a single label to enable blinding of the subjects and all site personnel (except for the designated unblinded dispensing pharmacist).

7.3.3 Secondary Packaging and Labelling Information (Bulk Packaging)

Table 13 Description of Boxes

Drug Supplies	Individual Box Contents
Blinded	[redacted] per box

Each shipping package will be labelled with a single label printed with black ink and may include the following text:

Protocol # Kit # Lot # (Packaging Lot Trace ID) Visit # Expiration date Kit contents Product identifiers (name and strength)	Route of administration Directions for use Caution statement (to be used by qualified Investigators only) Storage conditions Sponsor name, address, and telephone number Country regulatory requirements

ID=identification; #=number.

7.3.4 Product Storage

UPB-101 should be stored at -20°C ±5°C. The stability of the UPB-101 has been evaluated at -20°C ±5°C (for 36 months) and at 5°C ±3°C (for 6 months) and the product was found to be stable under these conditions.

7.3.5 Preparation

UPB-101 vials should be placed at room temperature until fully thawed upon visual inspection. Once transferred to a syringe for SC injection, the syringe should be allowed to reach room temperature for approximately 1 hour prior to administration.

7.4 Treatment Assignment

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.

7.5 Blinding

Subjects, Investigators, all site personnel (except for the designated unblinded dispensing pharmacist and flow cytometry laboratory personnel) and the blinded CRO team will be blinded to study drug.

The following procedures have been instituted to mitigate the risk of unblinding 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 other study subjects (note: site personnel performing dosing may be blinded site personnel, provided all conditions within this section are met).
- The IXRS will be used to control all drug distribution and inventory for this study.

The Sponsor will be unblinded throughout this exploratory study but will not be involved 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 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 (Section 5.8.2). These reports will not contain any unblinded individual PK results. In addition, summary data that might bias blinded personnel will also be inaccessible to blinded parties.

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.

7.5.1 Emergency Unblinding of Treatment Assignment

The IXRS will be programmed to allow an Investigator to unblind subjects and to unmask drug identity. When the Investigator contacts the system to unblind a subject, he/she must provide the requested subject identifying information and confirm the necessity to unblind the subject. The Sponsor will not provide a disclosure envelope with the clinical supplies.

The Investigator may unblind a subject's treatment assignment only in the case of an emergency when immediate knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject.

The decision to unblind must be that of the Investigator or delegated treating physician. Authorization from the Sponsor (or designee) is not required. Whenever possible, the

Investigator is encouraged to discuss options with the Sponsor's blinded Medical Monitor or appropriate study personnel before unblinding the subject's treatment assignment so long as this incurs no delay. If this is impractical, the Investigator must notify the Sponsor and/or Sponsor's blinded Medical Monitor as soon as possible, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be recorded in the appropriate data collection tool.

8 ADVERSE EVENTS

8.1 Performing Adverse Event Assessments

The Investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's eCRF. If the AE is "unexpected," the Investigator must report the AE immediately to Sponsor or its designee. In addition, certain AEs (as described in Section 8.9) are classified as "serious" and must be reported no later than 24 hours after the Investigator recognizes/classifies the event as an SAE to the Sponsor or its designee.

In the case of SAEs, the Investigator may discontinue the subject from treatment prematurely but should discuss with the blinded Medical Monitor beforehand where possible.

8.2 Adverse Event Definitions

The following definitions of terms are guided by the ICH, the US Code of Federal Regulations (21 Code of Federal Regulations 312.32) and EU Directive 2001/83/EC and are included herein.

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Adverse events include, but are not limited to:

- Any symptom or condition not previously reported by the subject (medical history).
- An exacerbation of a pre-existing symptom or condition.
- A significant increase in frequency or intensity of a pre-existing episodic event or condition.
- A drug interaction.
- A condition first detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.

An AE does not include:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, blood transfusion); the condition that leads to the procedure is an AE (e.g., bleeding oesophageal varices, dental caries).

- Overdose of either study drug or concurrent medication without any clinical signs or symptoms.

- Non-clinically significant abnormal laboratory values. (If accompanied by signs/symptoms, the signs or symptoms are considered an AE).

8.3 Pre-randomization Adverse Events

Adverse events that occur between the time subject signs the ICF for the study and the time when that subject is randomized will be summarized as medical history and not as an AE unless the event meets the definition of an SAE as defined in Section 8.9.

8.4 Severity

The Investigator must categorize the severity of each AE according to the following guidelines:

Mild: Associated with no limitation of usual activities or only slight discomfort; generally, not requiring alteration or cessation of study drug administration; and/or not needing therapeutic intervention.

Moderate: Associated with limitation of usual activities or significant discomfort; generally requiring alteration or cessation of study drug administration; and/or requiring therapeutic intervention.

Severe: Associated with inability of subject to carry out usual activities or very marked discomfort; considered to be life-threatening; resulting in significant disability or incapacity; and requiring therapeutic intervention.

8.5 Relationship

The relationship of each AE to the study drug administration will be assessed by the Investigator after careful consideration, and according to the following guidelines:

Definitely: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug; it disappears or decreases on cessation or reduction in study drug dose; and/or it reappears or worsens when the study drug is administered.

Probably: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug; and/or that could not be reasonably explained by other factors such as underlying disease, complications, concomitant drugs, or concurrent treatments.

Possibly: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug, but that could reasonably have been produced by a number of other factors including underlying disease, complications, concomitant drugs, or concurrent treatments.

Not Related: A reaction for which sufficient data exist to indicate that the aetiology is unrelated to the study drug.

8.6 Outcomes of Adverse Events

Outcome data will be collected for each AE. Options for terms to be applied will include resolved, recovered with minor sequelae, recovered with major sequelae, or unresolved.

8.7 Adverse Events of Special Interest

Certain AEs have been identified as AEs of special interest (AESIs) due to the class of drugs being studied. These AEs will be captured through spontaneous reporting in the eCRF and the reporting of these AESIs will be described in the SAP. An AESI may be serious or non-serious. For this study, AESIs based on the class of drugs include:

- Allergic reactions.
- Immune complex disease.
- Severe infections which are defined as:
    - Life threatening or,
    - Requiring hospitalization or,
    - Requiring treatment with antiviral medications, IV antibiotics or medications for helminth parasitic infection or,
    - Requiring a permanent discontinuation of study drug.
- Injection site reactions.

8.7.1 Management of Injection Site Reactions

Subjects will be monitored for unusual signs and symptoms of injection site reactions such as pain, localized swelling, tenderness, or erythema.

If a subject experiences an injection site reaction, pre-medication including acetaminophen and/or antihistamine, may be administered per institutional standard at the discretion of the Investigator.

Use of an infusion pump may also be considered to reduce a subject's injection site reactions at the discretion of the Investigator.

8.8 Clinical Laboratory Adverse Events

Laboratory abnormalities observed during the study that are associated with a medical condition will be reported under the AE for that condition. For example, significantly elevated creatinine may be included under renal failure. Isolated laboratory abnormalities should be reported as AEs if they are deemed clinically significant by the Investigator.

Criteria for a "clinically significant" laboratory abnormality are:

- A laboratory abnormality that leads to a dose-limiting toxicity (e.g., an abnormality that results in study drug dose reduction, suspension, or discontinuation).
- A laboratory abnormality that results in any therapeutic intervention (i.e., concomitant medication or therapy).
- Other laboratory abnormality judged by the Investigator to be of clinical concern (e.g., significant fall in haemoglobin not requiring transfusion).

For laboratory abnormalities that do not meet the above criteria but are outside of normal reference range, the Investigator should indicate whether the value is clinically significant or not clinically significant for the subject.

8.9 Serious Adverse Events

An AE is considered "serious" if, in the view of the Investigator or Sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening AE.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse.

Hospitalization for a pre-existing condition, including elective procedures, which has not worsened, does not constitute an SAE.

An AE or suspected adverse reaction is considered "life-threatening' if, in the view of the Investigator or Sponsor, its occurrence places the subject or subject at immediate risk of death. It does not include an adverse reaction or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

An AE or suspected adverse reaction is considered unexpected if it is not listed in the current IB or is not listed at the specificity or severity that has been observed.

8.9.1 Reporting of Serious Adverse Events

All SAEs or serious pre-treatment events that occur during the course of the study must be promptly reported by the Investigator to tranScrip. Deaths and AEs assessed as life-threatening are to be reported immediately and SAEs that meet other criteria are to be reported within 24 hours from the point in time when the Investigator becomes aware of the SAE. All SAEs must be reported whether or not they are considered causally related to UPB-101. SAE forms will be completed, and the information collected will include subject number, a narrative description of the event, and an assessment by the Investigator as to the intensity of the event, criteria of seriousness, and relationship to study drug. Follow-up information on the SAE may be requested by the Sponsor or Medical Monitor.

Contact Information:

[redacted]

If there are serious, unexpected adverse drug reactions associated with the use of study drug, the Sponsor will notify the appropriate regulatory agency and all participating investigators on an expedited basis. The local Institutional Review Board (IRB)/IEC will be promptly notified based on local regulations where required by the IRB/IEC of all serious, unexpected adverse drug reactions involving risk to human subjects.

All AEs, whether serious or not, will be described in the source documents and in the appropriate section of the eCRF. All AEs and SAEs, including those that worsen in intensity or outcome of event or frequency relative to baseline, that occur after signing the ICF until Day 225 / Final Visit, must be recorded. Adverse events that are ongoing at the time of treatment discontinuation should be followed for a minimum of 90days after the last dose of study drug or the Final Visit whichever is later.

Information to be reported in the description of each AE includes:

- A medical diagnosis of the event (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event should be recorded).
- The date of onset of the event.
- The date of resolution of the event, if applicable.
- Whether the event is serious or not (include criteria for seriousness).

- Medical history of the subject and concomitant medications.
- Details of any laboratory tests.
- Intensity of the event (refer to Section 8.4 for definitions).
- Relationship of the event to study treatment (refer to Section 8.5 for definitions).
- Action taken: none; change in the study drug administration (e.g., temporary interruption in dosing); drug treatment required; nondrug treatment required; hospitalization or prolongation of hospitalization required (complete SAE page); diagnostic procedure performed; subject discontinued from treatment (complete End-of-Treatment visit).
- Outcome: Recovered/Resolved, Recovering/Resolving, Not Recovered/Not Resolved/Ongoing, Recovered/Resolved with Sequelae, Fatal, Unknown (notify the Medical Monitor immediately and complete the SAE report form).

8.9.2 Supplemental Investigations of Serious Adverse Events

The Investigator and supporting personnel responsible for subject care should discuss with the Sponsor's Medical Monitor any need for supplemental investigations of SAEs. The results of these additional assessments conducted must be reported to the Sponsor. If a subject dies during participation in the study and a post-mortem examination is performed, a copy of the autopsy report must be submitted to the Sponsor.

8.9.3 Post-Study Follow-Up of Adverse Events

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. The Sponsor retains the right to request additional information for any subject with ongoing AEs/SAEs at the end of the study, if judged necessary.

8.9.4 Notification of Post-Study Serious Adverse Events

Investigators are not obligated to actively follow subjects after the completion of the study. SAEs after the Final Visit of the Observation Period do not need to be reported unless considered related to the study drug by the investigator, in which case the SAE should be reported to the Sponsor. All SAEs must be reported to the Sponsor no later than 24 hours after the Investigator recognizes/classifies the event as an SAE, as described in Section 8.9.1.

8.9.5 Independent Ethics Committee Notification of Serious Adverse Events

The Investigator is responsible for promptly notifying their IEC of all SAEs, including any follow-up information, occurring at their site and any SAE regulatory report, including any follow-up reports that he/she receives from the Sponsor. Documentation of the submission to the IEC must be retained for each safety report. As with all IEC communications, the Investigator must copy the Sponsor and is also responsible for notifying the Sponsor if their IEC requires revisions to the ICF or other measures based on its review of an SAE report.

8.9.6 Health Authority Safety Reports

The Sponsor or its representatives will submit a safety report to appropriate regulatory agencies of any suspected adverse reaction that is both serious and unexpected within the appropriate timeframe.

The Sponsor or its representatives will send the Investigator copies of each safety report submitted to regulatory agencies. Safety reports must be submitted to the appropriate IEC as per their requirements.

Documentation of all communications with the IEC and regulatory authorities must be retained for each safety report.

8.9.7 Overdose

An overdose is defined as a dose greater than the intended dose level assigned to the cohort. In the event of an overdose of study drug, the Investigator should use clinical judgment in treating the overdose and contact the Sponsor's Medical Monitor. The Investigator should refer to the relevant documents for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study drug being used in this study. Such documents may include, but not be limited to, the IB for study drug.

8.9.8 Pregnancy

To ensure subject safety, each pregnancy in a female subject from Screening until study completion must be reported to the Sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy should be recorded on a Paper Pregnancy Report Form and reported by the Investigator to the Sponsor's Clinical Safety Management or designee. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Sponsor study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported in the eCRF as per Section 8.9.1.

8.9.9 Paternal Exposure

If a male subject's partner becomes pregnant during the course of the study, it must be reported to the Sponsor within 24 hours of the Investigator learning of its occurrence.

8.9.10 Hy's Law

Cases where a subject shows an AST or ALT ≥3x ULN and TBL ≥2x ULN may need to be reported as SAEs. Please refer to Appendix 1 for further instructions in cases of combined increase of aminotransferase and TBL.

9 STATISTICAL CONSIDERATIONS

An outline of the key statistical methods follows; full details will be described in in the SAP.

9.1 Statistical Hypotheses

No formal statistical hypotheses will be tested in this safety study.

9.2 Sample Size Determination

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.

9.3 Populations for Analyses

The following analysis sets will be used for the planned analyses.

- Safety Population: Subjects who receive at least 1 dose of study drug.
- Pharmacokinetic Population: Subjects who receive at least 1 complete dose of study drug and for whom at least 1 PK parameter can be estimated.
- Pharmacodynamic Population: Subjects who receive at least 1 dose of study drug and have at least 1 post-baseline blood sample measured for biomarkers.

9.4 Statistical Analyses

9.4.1 General Considerations

All safety, immunogenicity, PK, and PD data will be listed by subject. Unless otherwise specified, baseline is defined as the last observed measurement, whether scheduled or unscheduled, prior to the first dose of study drug.

UPB-101 treatment groups will be defined based on the cohort and dose assignment (e.g., [redacted]). The placebo treatment group will include all subjects assigned to placebo and will be pooled according to dosing regimen (e.g., Placebo [redacted], Placebo [redacted]) or, where appropriate, across all study parts.

No analysis windows will be defined. Data for repeatedly measured endpoints will be analysed according to the nominal visit. Summaries will be grouped by study part to maintain visit alignment across treatment groups.

Continuous variables will be summarized by UPB-101 dose group and pooled placebo, and by dosing frequency with descriptive statistics (e.g., number of observations, mean, standard deviation, median, interquartile range, maximum, and minimum). Categorical variables will be tabulated by frequency and percent of subjects per UPB-101 dose group and pooled

placebo, and by dosing frequency. Demographic data will be summarized by treatment, dose, and dose regimen. Analyses will be based on observed data only; no data will be imputed.

9.4.2 Subject Disposition

The number of subjects who are randomized, treated, and complete the study will be tabulated by treatment group. The data on subject disposition and informed consent will be listed.

9.4.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics and listed. Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and listed.

9.4.4 Investigational Product Exposure

Number of injections and total dose received will be tabulated by treatment group. Reasons for incomplete and interrupted injections will be listed.

9.4.5 Prior and Concomitant Medications

All medications will be coded using WHODrug.

Background asthma medications are defined as medications taken for asthma at a stable dose during at least 3 months prior to randomization. Background asthma medications will be tabulated, and their duration summarized. Changes from the stable dose during the study will be listed.

Medication history, Screening concomitant medications, and post-dose concomitant medications will be tabulated by Anatomical Therapeutic Chemical class and preferred term.

9.4.6 Safety Analyses

All safety analyses will be conducted using the Safety Population.

MedDRA will be used to code verbatim terms of AEs. Adverse events will be summarized by system organ class, preferred term, and treatment group for the number and percent of subjects reporting AEs, the number of events, and the number of subjects with any AE. All AEs will be listed, including onset and resolution dates, verbatim term, preferred term, treatment, severity, relationship to treatment, action taken, and outcome. The pooled placebo group will be used in these summaries.

Absolute values and change from baseline physical examinations, clinical laboratory evaluations vital signs assessments, and ECG parameters will be summarized by visit and by treatment group. The frequency of subjects with safety laboratory results outside of normal reference ranges will be tabulated by treatment and visit. No inferential statistical analyses are planned for safety parameters. Placebo groups will not be pooled in these summaries.

9.4.7 Immunogenicity Analyses

Immunogenicity analyses will be conducted on the Safety Population.

Anti-drug antibody data will be listed for each subject. A selected ADA-positive sample for each subject who has ADA-positive results will undergo a confirmatory assay (NAb) to assess their neutralizing potential. Summaries of positive ADA test results over time and NAb test results may be provided.

9.4.8 Pharmacokinetic Analyses

All PK analyses will be conducted using the PK Population. Actual blood sampling time points will be used to evaluate the PK parameters.

Individual concentrations of UPB-101 will be displayed graphically and listed by treatment group. They will be summarized using the number of available observations, the number of values below the lower limit of quantification, mean, median, standard deviation, minimum, maximum, geometric mean, and geometric coefficient of variation (assuming log-normally distributed data). Descriptive statistics of concentrations will be calculated if at least one third of the individual data points are quantifiable (≥lower limit of quantification).

Dose proportionality information will be obtained by comparing PK parameters of UPB-101 across applicable dose levels. A model will be fitted using all doses and across all cohorts to assess dose proportionality for C_{max}, t_{max}, and AUC_{tau} after the first dose. Within each dosing regimen, dose proportionality using a comparison of C_{max} and AUC_{tau} after the last dose will also be assessed using descriptive statistics.

Immunogenicity, PD biomarkers and clinical outcome measures such as FEV_1, CGI-C and ACQ-7 will be explored across dose cohorts using dose and exposure-response modelling to assess for dose and/or exposure related trends.

9.4.9 Exploratory Analyses

Analysis of all exploratory PD endpoints (biomarkers, flow cytometry assays, CGI-C, ACQ-7, and FEV_1) will be fully described in the SAP.

9.4.9.1 Pulmonary Function Tests

Analysis of the spirometric data will be fully described in the SAP.

Baseline for spirometry will be defined as the mean of the 60-minute and 30-minute pre-dose values at Visit 4. On dosing days after Visit 4, these are the 60-minute and 30-minute pre-dose values. At subsequent (non-dosing) visits, morning trough FEV_1 will be defined as the mean of 2 measurements performed approximately 30 minutes apart. If one of the measurements is not available or conducted post-dose, the other value will be used as the morning trough FEV_1.

Change from baseline in morning trough FEV_1 will be summarized descriptively by visit and by treatment group.

9.4.10 Administrative Interim Analysis

An administrative interim analysis will be conducted when, at a minimum, Cohorts 1 and 2 are expected to have completed dosing. 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.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Regulatory Authority Approval

The Sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements prior to a site initiating the study in that country.

10.2 Ethical Conduct of the Study and Institutional Review Board or Independent Ethics Committee Approval

The study will be conducted in accordance with GCP. These standards respect the following guidelines:

- ICH (ICH E6 (R1) 1996).
- US Code of Federal Regulations dealing with clinical studies (21 Code of Federal Regulations Parts 50, 54, 56, and 312).
- World Medical Association Declaration of Helsinki (WMA).
- Any additional regulatory requirements.

The Investigator (or Sponsor, where applicable) is responsible for ensuring that this protocol, the site's ICF, and any other information that will be presented to potential subjects (e.g., advertisements or information that supports or supplements the ICF) are reviewed and approved by the appropriate IEC. The Investigator agrees to allow the IEC direct access to all relevant documents. The IEC must be constituted in accordance with all applicable regulatory requirements.

The Sponsor will provide the Investigator with relevant documents/data that are needed for IEC review and approval of the study. If the protocol, the ICF, or any other information that the IEC has approved for presentation to potential subjects is amended during the study, the Investigator is responsible for ensuring the IEC reviews and approves, where applicable, these amended documents. The Investigator must follow all applicable regulatory requirements pertaining to the use of an amended ICF including obtaining IEC approval of the amended form before new subjects' consent to take part in the study using this version of the form. The IEC approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to the Sponsor promptly.

10.3 Subject Information and Consent

The study will be conducted in accordance with applicable subject privacy requirements. The proposed ICF, which will comply with applicable regulations, must be reviewed and approved by the IEC and the Sponsor prior to initiation of the study.

The Investigator or designee will be responsible for obtaining written informed consent from potential subjects prior to any study-specific Screening and entry into the study. A copy of the signed ICF will be provided to the subject. The original will be retained by the Investigator.

Sites may opt to utilize a pre-screening consent form to enable complete blood count testing which includes the absolute eosinophil number, for consenting potential subjects while they consider the ICF for the full study. This pre-screening ICF will also be reviewed and approved by the IEC and Sponsor prior to use. The execution, dating, signing, copying, distribution, and filing of this ICF will be identical to the ICF of the main study. Pre-screening may occur no longer than 90 days prior to Screening Visit 1.

10.4 Laboratory Accreditation

Any laboratory facility intended to be used for analysis of clinical laboratory samples required by this protocol must provide evidence of adequate licensure or accreditation according to the prevailing regulations in that state and/or country. Reference values and/or normal ranges for the test results must be provided to the Sponsor. The Sponsor must be notified promptly in writing of any changes occurring in reference values during the study.

10.5 Confidentiality

10.5.1 Confidentiality of Data

By signing this protocol, the Investigator affirms to the Sponsor that information furnished to the Investigator by the Sponsor will be maintained in confidence and such information will be divulged to the IEC, or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this study will be considered confidential by the Investigator, except to the extent that it is included in a publication consistent with relevant clauses in Section 10.11.

10.5.2 Confidentiality of Subject Records

By signing this protocol, the Investigator agrees that the Sponsor (or representative), IEC, or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/CRF data. By signing the ICF, the Subject also agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the Subject will be identified by unique code only; full names/initials will be masked prior to transmission to Sponsor. In addition, the Investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable laws, rules and regulations.

10.6 Quality Control and Assurance

The Sponsor or their designee is responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure

that studies are conducted properly; data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP; and all applicable laws, rules, and regulations relating to the conduct of the clinical study.

10.7 Data Management

Data management procedures and information for this protocol will be provided by the Sponsor or their designee.

10.8 Study Monitoring

In accordance with applicable regulations, GCP, and the Sponsor (or its designee) procedures, the tranScrip's monitor (or designee) will contact the site prior to subject enrolment to review the protocol and data collection procedures with site staff. In addition, the monitor will periodically contact the site, including conducting on-site visits. The extent, nature, and frequency of on-site visits will be based on such considerations as the study objective and/or endpoints, the purpose of the study, study design complexity, and enrolment rate.

During these contacts, the monitor will:

- Check the progress of the study.
- Review study data collected.
- Conduct source document verification.
- Identify any issues and address their resolution.

This will be to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

The Investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

Upon completion of the study, the monitor will conduct the following activities in conjunction with the Investigator or site staff, as appropriate:

- Return of all study data to the Sponsor.
- Resolution of all data queries.

- Accountability, reconciliation, and arrangements for all investigational products.
- Review of site study records for completeness.

After the final review of the study files, the files should be secured for the appropriate time period as specified in Section 10.9. The Investigator will also permit inspection of the study files by the Sponsor's Quality Assurance auditors, and authorized representatives of the FDA or other applicable regulatory agencies.

In exceptional circumstances, related to restrictions due to COVID-19, the Sponsor, in agreement with the Principal Investigator and the hospital, may implement monitoring activities that may include, among others, remote source data verification. Remote source data verification involves sharing of study-related medical records/documents with the monitor electronically using a suitably controlled remote access method.

If remote monitoring is required, no copy of any source records will be collected by the monitor and no images will be recorded during the review.

10.9 Retention of Data

Documents that individually and collectively permit evaluation of the conduct of the study and the quality of the data produced must be maintained for review by the Sponsor's quality assurance auditors and by all applicable regulatory authorities. The period of time these documents must be maintained is governed by applicable regulations. The Sponsor or its designee will inform the Investigator when these documents may be destroyed. The Sponsor or its designee must be notified in writing at least 6 months prior to the intended date of disposal of any study record related to this protocol to allow the Sponsor to make alternate storage arrangements.

10.10 Financial Disclosure

The Principal Investigator or sub-Investigators named on the FDA Form 1572 or the locally accepted alternate Investigator Statement form, will need to complete a financial disclosure form prior to study initiation, at any time during the study execution if new information needs to be disclosed, and for 1 year after study completion. Investigators should make the IEC aware of any financial interests that the Investigator has in the investigational product.

10.11 Publication Policy

The Sponsor intends to publish the results of all clinical studies it sponsors in compliance with the Declaration of Helsinki (http://www.wma.net/en/10home/index.html). Consistent with the recommendations of the editors of several leading medical journals, the International Committee of Medical Journal Editors (ICMJE), authorship of publications resulting from Sponsor-sponsored studies should fairly recognize the activities of those that have made a significant contribution to the study. Thus, it is anticipated that authorship will reflect the contribution made by Sponsor personnel, the Investigators and others involved, such as statisticians.

In recent years, issues about conflicts of interest and accuracy of the study data have been raised in the medical press. Accordingly, the Sponsor has developed publication guidelines as described below:

1. **Responsibility:** Each Principal Investigator is responsible for the accuracy and completeness of all data from their site. The Sponsor (or its representatives) is responsible for the accuracy of the data entered into the study databases and for the accuracy of the analyses conducted.

2. **Authorship and Publication Committee:** The Sponsor, in collaboration with the Investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance with the principles of the ICMJE and the International Society for Medical Publication Professionals. It is anticipated that a publication committee will be formed to assume oversight of these activities. All manuscripts will be reviewed and agreed upon before submission for publication by all authors.

3. **Sponsor Review of External Manuscripts:** Consistent with the previous bullet point, drafts of any and all publications or presentations that may arise from this study must be submitted at least 30 days prior to submission for publication or presentation to the Sponsor for review, approval, and to ensure consistency with the policy in this protocol. The Sponsor will have the right to request appropriate modification to correct facts and to represent its opinions, or the opinions of the publication committee, if these differ with the proposed publication. Investigators will delete any Sponsor confidential information from the publication or presentation upon Sponsor's request.

4. **Confidentiality:** Investigators will conduct all interactions with the Sponsor and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of non-clinical studies, or chemical formulae) may still need to **remain confidential.**

5. **Medical Journal Review**: Consistent with the intention of the Sponsor to publish the study in a fair and accurate manner, the Sponsor supports diligence in the publication review process of medical journals. Accordingly, upon request, all pertinent study data and information will be made available as supplemental information for journal editors and reviewers to evaluate and audit, e.g., protocol and amendments, data tabulations. The journal and reviewers will need to make arrangements to maintain the confidentiality of such supplemental information, where relevant, and the Sponsor will make suitable arrangements to ensure that the identity of journal reviewers is kept confidential. Records will be maintained of reviewers and the respective documents and datasets that were reviewed by each of them.

6. **Reporting of Clinical Study Results:** To provide transparency in the conduct and reporting of randomized clinical studies, the Sponsor reports clinical findings based on the guidance of The Consolidated Standards of Reporting Trials Statement (Schulz, Altman et al. 2010) and a 25-item checklist which is intended to improve the

reporting of a randomized controlled study, and to facilitate reader understanding of the study design, conduct, analysis and interpretation, and to support their ability to assess the validity of its results.

7. **Internet Clinical Study Listing:** In addition, also consistent with the recommendations of the ICMJE, the Sponsor will make available appropriate information regarding the study via the internet. This will include registration and listing of the study on www.clinicaltrials.gov, the US National Institutes of Health listing of clinical studies, and other clinical study listings as appropriate (e.g., European Union Drug Regulating Authorities Clinical Trials Database; https://eudract.ema.europa.eu).

10.12 Annual Report

Upstream Bio will be responsible for preparing the Annual Report of the study status and submitting the Annual Report to the Regulatory Authorities in each country in which the study is conducted as well as to each of the IECs.

10.13 End of Study Notification and Submission of Summary Report

Upstream Bio is responsible for preparing and submitting the end of study notification to the Ethics Committees and Regulatory Authorities in the EU Member States in which the study has been conducted. This must be submitted within 90 days of the end of the study (15 days if the study is terminated early).

For this purpose, the end of the study (study completion) is defined as the Last Patient Last Visit. Any change to this definition is considered a significant amendment and MUST be notified to (and approval sought from) the Ethics Committees and the Regulatory Authorities concerned.

Upstream Bio will be responsible for preparing and submitting a summary of the Clinical Study Report to the regulatory authorities in each member state in which the study was conducted within 12 months of the end of the study. This report must follow the ICH E6 (R2) guideline (ICH E6(R2) 2016).

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12 APPENDICES

Appendix 1 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy that reveals an increase of serum aminotransferases ≥3 × ULN or bilirubin ≥2 × ULN should undergo detailed testing for liver enzymes using the study Chemistry panel defined in Table 10 which includes ALT, AST, alkaline phosphatase (ALP) and TBL. Testing should be repeated within 48 to 72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central laboratory to inform the Investigator, Sponsor's Medical Monitor, and study team when ALT, AST or TBL exceed the thresholds above. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate or severe by the Investigator where ULN:

	ALT or AST		**TBL**
Moderate	>3 × ULN	or	>2 × ULN
Severe†	>3 × ULN	and	>2× ULN

† Hy's Law Definition: Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10% to 50% mortality (or transplant). The 2 "requirements" for Hy's Law are:

- Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher than 3 ×ULN ("2 × ULN elevations are too common in treated and untreated subjects to be discriminating").

- Cases of increased bilirubin (at least 2 × ULN) with concurrent transaminase elevations at least 3 × ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert's syndrome (Temple 2006).

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST >8 × ULN.

- ALT or AST >5 × ULN for more than 2 weeks.

- ALT or AST >3 × ULN and International Normalized Ratio (INR) >1.5 (If INR testing is applicable/evaluated).

- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

The Investigator may determine that abnormal liver test results, other than as described above, may qualify as moderate or severe abnormalities, and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The Investigator or designee should complete the liver abnormality case report form (LA-CRF) that has been developed globally and can be activated for any study or another appropriate document (e.g., liver abnormality source consistent with the LA-CRF content). Subjects with confirmed abnormal liver test results should be followed up as described below.

Confirmed moderately abnormal liver tests should be repeated 2 to 3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.

Severe hepatic function abnormalities as defined above, in the absence of another aetiology, may be considered an important medical event and may be reported as an SAE. The Sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the Investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new-onset diseases should be recorded as “AEs” on the AE page. Illnesses and conditions such as hypotensive events and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Non-alcoholic steatohepatitis is seen in obese hyperlipoproteinemic and/or diabetic subjects, and may be associated with fluctuating aminotransferase levels. The Investigator should ensure that the medical history documentation captures any illness that predates clinical study enrolment that may be relevant in assessing hepatic function.

- Obtain a history of concomitant drug use (including non-prescription medications, complementary and alternative medications), alcohol use, recreational drug use, and special diets. Medications, including dose, should be entered on the concomitant medication page. Information on alcohol, other substance use, and diet should be entered on the LA-CRF or an appropriate document (e.g., liver abnormality page from the source).

- Obtain a history of exposure to environmental chemical agents.

- Based on the subject’s history, other testing may be appropriate including:

- Acute viral hepatitis (A, B, C, D, E or other infectious agents).
- Ultrasound or other imaging to assess biliary tract disease.
- Other clinical laboratory tests including INR, direct bilirubin.

- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible aetiology on the LA-CRF or an appropriate document (e.g., liver abnormality page from the source).

Study Discontinuation

In the absence of an explanation for increased liver tests, such as viral hepatitis, pre-existing or acute liver disease or exposure to other agents associated with liver injury, the subject may be discontinued from the clinical study. The Investigator may determine that it is not in the subject's best interest to continue clinical study enrolment. Discontinuation of treatment should be considered if:

- ALT or AST >8 × ULN.
- ALT or AST >5 × ULN for more than 2 weeks.
- ALT or AST >3 × ULN and TBL >2 × ULN or INR >1.5) (If INR testing is applicable/evaluated).
- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

In addition, if close monitoring of a subject with moderate or severe hepatic laboratory tests is not possible, clinical study drug should be discontinued.

References

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Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" issued by FDA on July 2009.

Appendix 2 Spirometry Performance

Spirometry data of the highest quality must be obtained for proper interpretation of the results of this protocol. To these ends, a standard spirometer will be used (provided by the Sponsor), central training provided, qualification will be required, and specific operating instruction will also be provided.

Methods for spirometry performance will be included in the spirometry laboratory manual.

Appendix 3 Sponsor Signature

Study Title: 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

Study Number: UPB-CP-01

Protocol Version: 9.0

Final Date: 31 March 2023

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Sponsor: Upstream Bio

Name: [redacted]

[redacted]

[redacted]

[redacted]

Appendix 4 Investigator's Signature

Study Title: 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

Study Number: UPB-CP-01

Protocol Version: 9.0 **Final Date:** 31 March 2023

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with the protocol and with any other study conduct procedures provided by the Sponsor.
- Not to implement any changes to the protocol without agreement from the Sponsor and prior review and written approval from the Institutional Review Board/ Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am aware of, and will comply with, Good Clinical Practices and all applicable regulatory requirements.
- That I am thoroughly familiar with the appropriate use of the investigational product, and other information provided by the Sponsor including, but not limited to, the following: the protocol and the current Investigator's Brochure (IB).
- To ensure that all persons assisting me with the study are qualified, adequately informed about the investigational product and of their study-related duties and functions.
- To supply the Sponsor with any necessary information regarding ownership interest and financial ties; to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study; and agree that the Sponsor may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- To report all information or data in accordance with the protocol and any other study conduct procedures provided by the Sponsor.
- That since the information in this protocol and IB is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited.
- To accurately transfer all required data from each subject's source document to the electronic case report forms (eCRFs). The eCRFs will be provided to the Sponsor in a timely manner at the completion of the study, or as otherwise specified by the Sponsor.
- To allow authorized representatives of the Sponsor or regulatory authority representatives to conduct on-site visits to review, audit, and copy study documents. I will personally meet with these representatives to answer any study-related questions.

Signature: _____ Date:_____

Name:_____ Site Name:_____

Site number: 0__

13 VERSION HISTORY

Version 4.0 of the protocol was the initial version approved by the MHRA/REC, changes to prior versions are not detailed below as they were not implemented at the study sites.

Version 9.0; 31 March 2023	
Change	Reason for Change
Protocol synopsis, Section 1.7 Study Posology, Section 3.1.1 Study Design: Cohorts, Section 7.2.1 Dosing Instructions Table 12 Clarification that Part B cohorts are adaptive and optional in nature and may not all be implemented.	Clarification
Protocol synopsis, Section 3.1.1 Study Design: Cohorts, Section 4 Study Population Selection and Withdrawal Criteria Approximate number of subjects update to 24 to 40 to reflect adaptive and optional nature of Part B cohorts.	Clarification
Protocol synopsis, Section 1.7 Study Posology, Section 7.2.1 Dosing Instructions Table 12, Figure 2: Study Design, Section 3.6.3 Cohorts with [redacted] Dosing Intervals, Section 7.2.4 Cohorts with [redacted] Dosing Intervals, Section 9.4.1 General Considerations Removal of the [redacted] dose for subjects in Cohort 4. Regimen changed from [redacted]	Change
Protocol synopsis, Section 3.1.2 Study Design: Periods, Section 3.7 Observation Period, Section 3.7.3 Cohorts with [redacted] Dosing Interval, Section 4.9.1 Duration of Study Participation Observation period for Cohort 4 amendment to 8 months following [redacted] dose.	Change
Protocol synopsis, Section 9.4.6 Safety Analyses Removal of detail relating to version of MedDRA to be used for the study This detail will be captured in the Data Management Plan.	Clarification
Table 8: Schedule of Events – Cohorts with [redacted] Dosing Interval Removal of the [redacted] dose for subjects in Cohort 4. Overnight admission and post-dose procedures will not be performed for this cohort.	Change
Section 6.1.4 Flow Cytometry Addition of statement that analysis of blood samples for pSTAT may be discontinued, based on assay status.	Addition
Section 9.4.11 Weeks 24 and 32 Analyses Removal of section related to monitoring and data management details related to Week 24 and Week 32 analysis. Monitoring and data management expectations are described in separate Monitoring and Data Management Plans, and analysis will be performed per standard practice.	Change

Version 8.0; 17 January 2023	
Change	Reason for Change
Protocol Synopsis, Section 3.1: Overall Study Design and Plan Extension of study period end date from May 2023 to October 2023.	Clarification/Correction
Protocol Synopsis, Section 7.2.1: Dosing Instructions, Table 12 Specification of dose level, frequency of administration and number of injections to achieve the dose for Cohort 4	Addition
Protocol Synopsis, Section 7.2.1: Dosing Instructions, Table 12 Addition of FeNO and blood samples for haematology including eosinophils to Visit 5 (D2), Visit 6 (D4), Visit 16 (D86), Visit 17 (D88), Visit 18 (D92) and Visit 19 (D99) for participants enrolled in Cohort 4.	Addition
Section 1.7: Rationale of Dose Regimen and Duration of Treatment – Local Tolerability Include injection information specific to the [redacted]mg dose	Addition
Section 1.7: Rationale of Dose Regiment and Duration of Treatment – Study Posology, and Section 3.1.1: Study Design: Cohorts Clarification to the timing of transition to Part B	Clarification/Correction
Section 3.1.3: General Considerations for Study Conduct Update to Cohort 4 portion of the study design figure to replace the generic Adaptive Design notation with the specific dose to be administered to participants in Cohort 4	Addition
Section 3.3: Schedule of Events, Table 5 Addition of FeNO and haematology with Eosinophils to visits 5 and 6 for participants in Cohort 4	Addition
Section 3.3: Schedule of Events, Table 8 Addition of FeNO and haematology with Eosinophils to visits 16, 17, 18, and 19 for participants in Cohort 4	Addition
Legend and footnotes for Table 4 through Table 8 Addition of footnotes m and n which provide instruction that FeNO ad haematology with Eosinophils performed at Visit 5, 6, 16, 17, 18 and 19 apply only to participants enrolled in Cohort 4	Addition
Section 7.2.1: Dosing Instructions Dose level of [redacted]mL to deliver [redacted] mg of UPB-101 added to clarify the volume of drug product to be administered at that dose. Information also added to specify the volume of placebo to be delivered for participants in the [redacted] mg cohort.	Addition

Version 7.0; 27 October 2022	
Change	Reason for Change
Synopsis, Section 1.6 Rationale of Study Design, Section 3.1 Overall Study Design and Plan, and Section 5.8 Safety Review Committee Removal of language related to parallel-sequential cohort approach, which enables subjects to be enrolled in cohort 3 prior to completion of cohort 2. Updates to language related to meetings for Safety Review Committee.	Clarification/Correction

Version 6.0; 14 September 2022	
Change	Reason for Change
Section 4.1 Inclusion Criterion 2: Upper age range limited changed from 55 to 60 years of age	Expand inclusion criteria
Section 4.1 Inclusion Criterion 5: Adjustment to the eosinophils criterion to allow subjects with 150 to 199 eosinophils cells/µL to be considered when FeNO is greater than 25 ppb at the same visit.	Expand inclusion criteria
Section 4.1 Inclusion Criterion 10: Requirement for participants to be fully vaccinated against Covid-19 removed.	No longer valid
Section 3.3 Schedule of events, Table 8: Visit window changed from ±3 days to ±5 days for later visits	Allow more flexibility
Protocol cover page: The blinded medical monitors contact telephone number replaced with a 24/7 cascade telephone number	Addition

Version 5.0; 18 August 2022	
Change	Reason for Change
Secondary Endpoints, Exploratory Endpoints: All references to Plasma UPB-101 concentrations corrected to Serum UPB-101 concentrations	Correction
Timing of PD and PK assessments (All Study Periods): Correction that requirements for all PD and PK assessments to be conducted between 6 AM and 10 AM does not apply to spirometry assessments. This allows the spirometry measurements to be collected at appropriate times relating to other assessments/dosing. Removal of duplicate wording where appropriate to improve clarity.	Correction/Clarification
Inclusion criteria: 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 CBP must either be sterile or their partner must use contraception	Clarification
Exploratory assessments; section 6.1.3: Remove serum when referring to total IgE measurements	Correction
Section 3.2, description of Screening Period	Clarification

Clarification that the Screening Period is defined as Day -21 to Day -1.	
Section 3.2 Study Activities Order of assessments updated to allow blood draws to occur earlier in the visit to minimise diurnal variations in the level of eosinophils.	Correction
Section 3.3 Schedule of events: Addition of explicit statement to allow procedures for Visit 1 to be conducted across multiple days.	Clarification
Section 3.3 Schedule of events, Table 4 Removal of requirement to perform CGI-C assessment prior to dosing. This assessment records the change in the asthmatic's status since the baseline and is therefore not appropriate prior to dosing.	Correction
Section 3.3 Schedule of events, Table 6, Table 7 and Table 8 COVID testing added for Day [redacted] for [redacted] and [redacted] cohorts and for Days [redacted] and [redacted] for [redacted] cohorts.	Correction
Section 3.3 Schedule of events Table 7: Samples for future analysis of additional cytokines added for [redacted] cohorts, Day 10	Correction
Section 3.3 Schedule of events Table 8: Visit window of ±3 days added for D127 and D155 for [redacted] cohorts	Correction
Section 3.3 Schedule of events Table 4 to Table 8 Addition of footnote h to ACQ-7 assessments On days where Spirometry is not performed, ACQ-7 question 7 will be completed by the investigator based on the FEV_1 value from the first measurement on the following morning. Note: footnote letters are reassigned as needed to accommodate the new footnote h.	Addition
Section 4.3 Future Cohort Eligibility 12. 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
Section 4.4 Re-screening Criteria Clarification to process for repeating of tests that may be remedied with time when enrolment criteria are initially failed.	Clarification
Section 5.4.6 Clinical Laboratory Assessments Clarification that eosinophil data will be provided to sites during screening but not afterwards.	Clarification/Addition

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.	
Section 6.2.1 Asthma Clinical Global Impression of Change Clarification that baseline for assessment is Day -1. CGI-C is an assessment of the change vs. that baseline and is therefore not required on or prior to Day -1.	Clarification/Correction
Section 6.2.2 Asthma Control Questionnaire Addition that if the ACQ is to be performed on a day without FEV1 predicted assessment, question 7 will be completed by the investigator based on FEV1 value from the first measurement on the following morning.	Addition
Section 7.5 Blinding Clarification that blinded site personnel may dose subjects provided all of the blinding conditions are met	Clarification
Section 7.5.1 Emergency Unblinding of Treatment Assignment Clarification that the Investigator is encouraged to discuss options with the blinded Medical Monitor and to notify the blinded Medical Monitor as soon as possible.	Clarification
Appendix 1: Liver Safety Monitoring and Assessment: Clarification to process of delivery of liver safety monitoring alerts from central laboratory and assessment of the parameters by the Investigator	Clarification