CLINICAL STUDY PROTOCOL

Sponsor's Reference Number: UPB-CP-02

Richmond Pharmacology Study Number: C22031

EudraCT Number: 2022-002698-26

IRAS ID: 1006619

TITLE:	A Randomized, Open-label, Parallel-group, Ethno-bridging Study Comparing the Pharmacokinetics and Safety of a Single Dose of UPB-101 in Healthy Japanese and Non-Japanese Non-East Asian Adults
PHASE:	Phase 1
DRUGS:	UPB-101
SPONSOR:	Upstream Bio, Inc.
PRINCIPAL INVESTIGATOR:	[redacted] Richmond Pharmacology Ltd. Telephone: [redacted] Fax: [redacted]
STUDY CENTRE:	Richmond Pharmacology Ltd. 1a Newcomen Street, London Bridge, London SE1 1YR, UK
Protocol Version and Date:	Version 1.0 17 OCT 2022

Information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical/regulatory review of the study, without written authorization from Upstream Bio or its affiliates.

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PROTOCOL APPROVAL SIGNATURE

Version 1.0, dated 17 October 2022

Sponsor's Approval

This protocol has been approved by Upstream Bio.

Sponsor's Signatory:

Name: [redacted], **MD**

[redacted]

Signature: [redacted] **Date:** 17 October 2022

INVESTIGATOR'S AGREEMENT

I have read this Upstream Bio Protocol No. UPB-CP-02:

A Randomized, Open-label, Parallel-group, Ethno-bridging Study Comparing the Pharmacokinetics and Safety of a Single Dose of UPB-101 in Healthy Japanese and Non-Japanese Non-East Asian Adults

I have fully discussed the objectives of this study and the contents of this protocol with Upstream Bio representative(s).

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical/regulatory review of the study, without written authorization from Upstream Bio. It is, however, permissible to provide information to a participant to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with ICH guidelines on GCP and with the applicable regulatory requirements.

I understand that Upstream Bio may decide to suspend or prematurely terminate the study at any time for any reason as described in the Master Service Agreement or Work Order with the clinical study site; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to Upstream Bio.

Principal Investigator:

[redacted]

Signature: [redacted] **Date:** 18 Oct 2022

STUDY PERSONNEL

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Principal Investigator	[redacted]

LIST OF ABBREVIATIONS

For the purposes of this protocol, 'Investigator' refers to the Principal Investigator or their delegate.

Ab	Antibody
ABPI	Association of the British Pharmaceutical Industry
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALS	Advanced life support
ALT	Alanine aminotransferase
AR	Adverse reaction
AST	Aspartate aminotransferase
$AUC_{0\text{-}inf}$	Area under the serum concentration-time curve from time 0 extrapolated to infinite time
$AUC_{0\text{-}t}$	Area under the serum concentration curve from time zero up to the last quantifiable concentration
$\%AUC_{extrap}$	Percentage of AUC that is due to extrapolation from t_{last} to infinity
BMI	Body mass index
CI	Confidence interval
CL/F	Total body serum clearance after dosing
C_{max}	Maximum observed concentration
COVID-19	Coronavirus disease 2019
CPMP	Committee for Proprietary Medicinal Products
CRF	Case report form
CRP	C-reactive protein
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events

CV	Coefficient of variation
D	Day
DBP	Diastolic blood pressure
DHP	Data handling protocol
DHP STW	Data handling protocol scheduling time windows
DoA	Drugs of abuse
DSUR	Development safety update report
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FDA	Food and Drug Administration
FeNO	Fractional exhaled nitric oxide
FIH	First in human
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
HBC	Hepatitis B core
HBsAg	Hepatitis B surface antigen
β-HCG	Beta human chorionic gonadotropin
HCV	Hepatitis C virus
HED	Human equivalent dose
Hep	Hepatitis
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's brochure
ICF	Informed consent form

ICH	International Council on Harmonization
ID	Identification
IFN λ	interferon gamma
IgE	Immunoglobulin E
IgG1	Immunoglobulin G1
IL-	Interleukin-
IMP	Investigational medicinal product
IMPD	Investigational medicinal product dossier
IP-10	interferon gamma-induced protein 10
INR	International normalized ratio
IV	Intravenous
λz	Terminal rate constant (slope of the serum concentration-time curve)
LFT	Liver function test
LLOQ	Lower limit of quantification
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
mRNA	Messenger ribonucleic acid
MTS	Master treatment schedule
Nab	Neutralizing antibodies
NHS	National Health Service
NJNEA	Non-Japanese non-East Asian
NOAEL	No observed adverse effect level
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
PT	Prothrombin time
QC	Quality control
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
QFT-G	QuantiFERON®-tuberculosis Gold
QP	Qualified Person
QTc	QT interval corrected
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
REC	Research ethics committee
RP	Research physician
RPL	Richmond Pharmacology Ltd
RSI	Reference safety information
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SmPC	Summary of product characteristics
SOC	System Organ Class
SOM	Study operations manual
SOP	Standard operating procedure
SRC	Safety review committee
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
$t_{1/2}$	Terminal elimination half-life
TARC	thymus activation regulated chemokine
TB	Tuberculosis

TEAE	Treatment-emergent adverse event
Th2	T helper 2
t_{max}	Time at which the maximum observed concentration occurs
TSLP	Thymic stromal lymphopoietin
TSLPR	Thymic stromal lymphopoietin receptor
UK	United Kingdom
ULN	Upper limit of normal
US	United States
USM	Urgent safety measures
V_z/F	Apparent volume of distribution estimated from the terminal elimination phase after dosing
W	Week
WOCBP	Women of child-bearing potential

STUDY SYNOPSIS

Protocol Reference: UPB-CP-02	**Study drugs:** UPB-101	
Title of the study: A Randomized, Open-label, Parallel-group, Ethno-bridging Study Comparing the Pharmacokinetics and Safety of a Single Dose of UPB-101 in Healthy Japanese and Non-Japanese Non-East Asian Adults		
Principal Investigator: [redacted]		
Study centre: Richmond Pharmacology Ltd. 1A Newcomen Street, London Bridge, London SE1 1YR, UK		
Study parts: N/A	**Clinical phase:** 1 (the study does not have therapeutic or prophylactic intent and does not plan to assess efficacy)	
Objectives	**Endpoints**	**Statistical analyses**
Primary		
To characterize and compare the pharmacokinetics (PK) of single doses of UPB-101 in healthy Japanese and Non-Japanese Non-East Asian (NJNEA) adults.	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 from time zero up to the last quantifiable concentration (AUC_{0-t}). If appropriate, area under the concentration-time curve from the time of dosing extrapolated to time infinity (AUC_{i0-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 (Vz/F), will also be analyzed. These endpoints will be assessed from baseline through Day 85 ±5 days in the PK Set.	Non-compartmental analysis will be used for estimation of pharmacokinetic parameters. The following pharmacokinetic parameters will be calculated using serum concentrations and actual sampling times: C_{max}, t_{max}, λz, $t_{1/2}$, AUC_{0-inf}, AUC_{0-t}, $\%AUC_{extrap}$, CL/F, Vz/F. Serum concentrations and PK parameters will be listed and summarized using descriptive statistics.

Secondary		
To assess and compare the safety and tolerability of UPB-101 in healthy Japanese and NJNEA adults.	The safety and tolerability endpoints will include adverse events (AEs), serious AEs (SAEs), physical examinations, clinical laboratory assessments, vital signs, electrocardiograms (ECGs) including telemetry, withdrawal of participants, and early terminations. These endpoints will be assessed from baseline through Day 85 ±5 days in the Safety Set.	AE data will be listed and summarized using descriptive statistics: the number (and %) of participants who had any AEs and the number of AE episodes will be summarized by each treatment group, and by each population (i.e., Japanese vs NJNEA). Laboratory, ECG and Vital Signs data will be listed and summarized descriptively (using absolute values along with change from baseline) by each treatment group. All participants will be included in the summary of participant disposition. This will present the overall number of participants, the frequency and percentage of participants randomized and treated, and who completed or discontinued from the study, along with reason for discontinuation.
To assess and compare the immunogenicity of UPB 101 when administered to Japanese and NJNEA adults.	UPB-101 anti-drug antibodies (ADAs) and neutralizing antibodies (Nabs). These endpoints will be assessed from baseline through Day 85 ±5 days in the Immunogenicity Set.	Immunogenicity (ADA and Nabs) to UPB-101 will be explored (incidence and duration) for each treatment group.
Exploratory		
To assess the pharmacodynamic (PD) effect of UPB-101 on biomarkers related to inflammation, specifically the thymic stromal lymphopoietin (TSLP) pathway.	Specific PD biomarkers for exploratory analysis will be selected based on relevant data from ongoing clinical studies.	Results will be summarized with descriptive statistics (e.g., number of observations, mean, standard deviation, median, and range). Absolute values and change from baseline will be summarized by visit and by treatment group.

Study design

A randomized, open-label, parallel group, ethno-bridging study comparing the pharmacokinetics and safety of a single dose of UPB-101 in healthy Japanese and NJNEA adults.

The study will include 4 planned dosing treatment groups. Treatment groups 1, 2 and 3 will consist of Japanese adults who will be administered a single subcutaneous (SC) dose of [redacted] mg, [redacted] mg or [redacted] mg of UPB-101, respectively. Treatment group 4 will consist of NJNEA participants who will receive a single SC dose of [redacted] mg UPB-101. All treatment groups will enrol and run in parallel. Japanese participants will be enrolled and randomized on Day 1 into treatment groups 1, 2 or 3 and NJNEA participants will be assigned to treatment group 4.

8 participants will be enrolled per treatment group, all will receive a single dose of UPB-101. Thus, a total of 32 male and female participants will be enrolled in the study (24 Japanese participants in treatment groups 1-3 and 8 NJNEA participants in treatment group 4).

The terms 'Japanese' and 'NJNEA' are described in the Inclusion Criteria (Section 5.3).

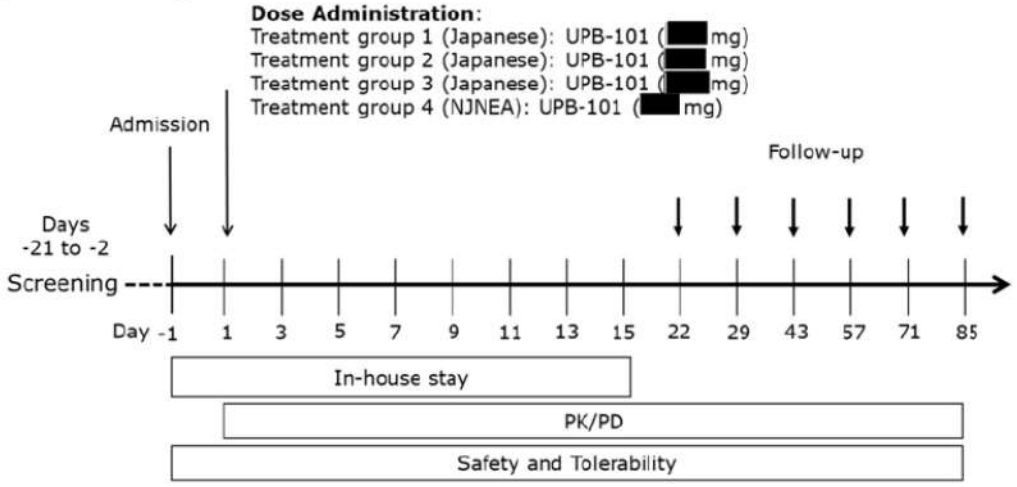
The 4 treatment groups will be assigned as few cohorts as operationally feasible to avoid period bias, and each cohort will attempt to contain at least 2 participants from each treatment group.

Table 1: Planned treatment groups

Planned Treatment Groups	Participants Ethnicity (N Participants)	Treatment	Number of Injections to Achieve Dose	Number of Doses
1	Japanese (8)	UPB-101 [redacted] mg SC	[redacted]	Single dose
2	Japanese (8)	UPB-101 [redacted] mg SC	[redacted]	
3	Japanese (8)	UPB-101 [redacted] mg SC	[redacted]	
4	Non-Japanese Non-East Asian (8)	UPB-101 [redacted] mg SC	[redacted]	

The study consists of 4 phases: screening, admission, dose administration, and follow-up. Initial eligibility will be evaluated during the screening phase. Final eligibility will be confirmed during the admission phase, prior to dosing.

Figure 1: Study flow chart



Following signing of the informed consent, participants will be evaluated for eligibility during the screening window from Day-21 to Day-2 and undergo a screening 24-hour Holter electrocardiogram (ECG). Eligible participants will be admitted on Day-1 for safety assessments and to confirm eligibility. Participants who remain eligible on the morning of Day 1 will be allocated to their respective treatment groups. Japanese participants will be randomized to treatment group 1, 2 or 3, and NJNEA participants will be allocated to treatment group 4. On the morning of Day 1, participants will undergo pre-dose procedures (including 12-lead ECG collection, PK and PD blood samples) and then receive a single SC dose of UPB-101. After dosing on Day 1, participants will undergo further 12-lead ECG collection and safety monitoring assessments. Participants will remain in-house through to Day 15 during which time they will continue to undergo 12-lead ECG collection time-matched to PK sampling, as per the Schedule of Assessments. Participants will then be discharged on Day 15 and followed up to Day 85 (approximately 5 half-lives of UPB-101 whose mean $t_{1/2}$ is [redacted] days) for evaluation of safety, tolerability, PK, PD, and immunogenicity. WOCBP will be asked to inform the Investigator if they

become pregnant between Day 85 and Day 120. Male participants with a partner of WOCBP will be asked to inform the Investigator if their partner becomes pregnant between Day 85 and Day 120. A home pregnancy testing kit will be issued to participants who are WOCBP to be used on Day 120 post-dose who will be asked to report the result to the Investigator.

Number of participants

Recruitment will aim to: enrol approximately 32 healthy adult males or females, achieve a 60:40 gender ratio (a minimum of 40% of participants from each gender), and include 2-3 non-Caucasian participants in the NJNEA treatment group.

Main criteria for inclusion:

Healthy males or females aged 18 to 40 years with BMI between 18 to 25 kg/m^2 at Screening. Participants in treatment groups 1 to 3 must have been born in Japan and hold a Japanese passport, with all 4 grandparents Japanese, and not living for more than 5 years outside of Japan. Participants in treatment group 4 must be NJNEA, i.e., not from East Asia [Japanese, Chinese, Korean, Mongolian, or Taiwanese]). All participants must agree to use highly effective methods of contraception (detailed in Section 5.5.1).

Main criteria for exclusion:

Current or recurrent disease (or condition), which may put the participant at risk, influence the results of the study, or otherwise affect their ability to participate in the study. Vital signs consistently outside the normal range at Screening or Day -1 and any other abnormal findings or vital signs, ECG, telemetry, physical examination or laboratory evaluation of blood and urine samples that the Investigator judges as likely to interfere with the study or pose an additional risk in participating. Previous exposure or current infection with hepatitis B, C and tuberculosis (TB); recent infection or vaccination; or a history of any untreated or unresolved infection, including parasitic infection.

Anticipated test treatment(s) and mode of administration

A single dose of [redacted], [redacted] or [redacted] mg of UPB-101 administered SC in the fasted state on Day 1.

Sample Size Considerations

The primary objective of the study is to characterize and compare the PK of single doses of UPB-101 in healthy Japanese and NJNEA adults. A sample size of 8 Japanese participants enrolled in each of treatment groups 1, 2, and 3 to be administered [redacted], [redacted], and [redacted] mg of UPB-101, respectively, and 8 NJNEA participants assigned [redacted] mg of UPB-101 to treatment group 4, is considered adequate to accomplish the primary objectives of the study. The sample size is not based on formal statistical hypothesis testing. A single treatment group of NJNEA participants is included to provide a comparison to the wider dataset. Data from this study may also be used to compare with the PK and safety data collected from the completed single ascending dose (SAD) study in healthy adult volunteers and the currently ongoing multiple ascending dose (MAD) study in adult asthmatics.

1. INTRODUCTION

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.

Indication

UPB-101 is a biologic under development for the treatment of adults with asthma. UPB-101 was previously known as 'ASP7266' but for consistency it will only be referred to as UPB-101 throughout this Clinical Study Protocol (CSP).

Asthma and thymic stromal lymphopoietin (TSLP)

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). TSLP 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.

Background to current asthma management

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. Most 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 two 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 participants 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 hyper-responsiveness. This suggested that differential regulation of expression of the TSLP gene might influence

susceptibility to asthma (He, Hallstrand et al. 2009). Nonclinical 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 (mRNA) and protein were increased in the airways of participants with asthma, as compared with healthy participants. Further, levels of TSLP mRNA were increased in participants 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 2021).

Background of the investigational medicinal product (IMP)

In 2003, Xolair (omalizumab) became the first biologic licensed for asthma. As an inhibitor of IgE, Xolair targets patients with allergic asthma. With some overlap in this patient 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 patients with an eosinophilic phenotype or those with oral corticosteroid-dependent asthma, through targeting of IL-13 and IL-4. Finally, in December 2021 the first TSLP inhibitor (tezepelumab) gained approval for the treatment of severe asthma.

Tezepelumab is a fully human monoclonal antibody that targets and blocks the TSLP ligand. 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 participants 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 patients with asthma.

While tezepelumab binds to the TSLP ligand, UPB-101, a novel recombinant fully human IgG1 monoclonal antibody, targets the TSLP receptor (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 I 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 nonclinical *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.

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).

As discussed previously, there are several biologics licensed for the treatment of asthma. However, these are limited to the treatment of allergic (omalizumab) and eosinophilic asthma (mepolizumab, reslizumab, benralizumab and dupilumab). Furthermore, these products are for 'severe' asthmatics and adoption is limited by high cost and payer access.

Despite the availability of several treatments that have been proven to be effective in most patients, 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 to ensure optimal treatment of asthma severities, 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).

Summary of pre-clinical and clinical experience (Including Safety, Pharmacokinetics, Pharmacodynamics)

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 in a Phase 1 unit in the United States under an FDA Investigational New Drug application.

Study 7266-CL-0001 was a randomized, double-blinded, placebo-controlled, single ascending-dose (SAD) study to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of UPB-101 in healthy adult male and female participants.

All doses were safe and well-tolerated. [redacted]

[redacted]

Please see the Investigator's Brochure for more information.

Ongoing Clinical Studies

Clinical study UPB-CP-01 is a two-part Phase 1, multi-centre, randomized, double-blind, placebo-controlled, multiple ascending-dose (MAD) study to assess the safety, tolerability, immunogenicity, PK, and PD of UPB-101 administered SC to adult participants with asthma. The study is being conducted in the UK.

The study consists of Part A and Part B. Part A includes 3 treatment groups with pre-set dosing regimens: [redacted] mg [redacted], [redacted] mg [redacted], and [redacted] mg [redacted]. Part B includes 2 adaptive design treatment groups whose doses and dosing intervals will be decided based upon the safety and PK results from Part A available to the unblinded Sponsor. This study was approved by the MHRA in June 2022 and is currently recruiting. To date, no SAEs or Adverse Events of Special Interest (AESI) have been reported. All [redacted] participants in the [redacted] mg [redacted] cohort have received at least 1 dose, several have received 2 doses,

and [redacted] received 3 doses of study drug ([redacted] active UPB-101 and [redacted] placebo). In addition, [redacted] participants in the [redacted] mg [redacted] cohort have received their first dose.

1.1 Rationale for conducting study

The findings cited in the Asthma and TSLP section above 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 participants (Study 7266-CL-0001). Overall, single ascending-doses of UPB-101 from [redacted] were considered safe and well-tolerated in healthy male and female participants. Based on that study a multiple ascending-dose clinical study (UPB-CP-01) is being conducted in the UK in participants with asthma.

The current study is an ethno-bridging PK study whose primary objective is to characterize and compare the PK of a single dose of UPB-101 in healthy Japanese and non-Japanese non-East Asian (NJNEA) adults. The main aim is to observe the effect (if any) of Japanese ethnicity on the PK of a single dose of UPB-101 administered subcutaneously, compared to NJNEA healthy adults. The data from this study will also be compared with that obtained from the completed first-in-human (FIH) study 7266-CL-0001 and the currently enrolling MAD study in asthmatics (UPB-CP-01) to guide the further clinical development of UPB-101 as a treatment for asthma.

1.2 Risk-benefit evaluation

1.2.1 Potential benefits

UPB-101 will be given to healthy participants for research purposes only. It is not anticipated that participants will receive any medical benefit apart from a general health examination.

1.2.2 Potential risks

1.2.2.1 UPB-101

The safety of UPB-101 is discussed above in the Summary of pre-clinical and clinical experience section. System Organ Class (SOC) specific risks and mitigation strategies are described below in the Section 1.2.2.2 Risk Management, particularly Table 2. Potential risks will be closely monitored for as part of the safety evaluations being performed in this study.

Of the [redacted] participants randomized in study 7266-CL-001, [redacted] ([redacted] out of [redacted]) and [redacted] ([redacted] out of [redacted]) of participants who received UPB-101 or placebo respectively experienced treatment-emergent adverse events (TEAEs). None of these were dose- or route-related, and less than half of these were judged by the investigator to be possibly related to UPB-101. [redacted]

[redacted]

1.2.2.2 Risk management

This study will be conducted at an accredited Phase 1 clinical study unit by an experienced Investigator and well-trained medical staff and technical staff with ample experience in the conduct of early phase clinical studies. The study has been designed to safely include suitable participants and to monitor, treat and communicate potential AEs and Adverse Reactions (AR).

Although not expected, participants will be closely monitored for potential SAEs.

The risk mitigation measures are summarized below in Table 2.

Table 2: Clinical and nonclinical known risks and mitigation features

Target System	Effect	Risk Mitigation
Renal System	1) No effects noted in human studies. 2) [redacted]	1) Standard monitoring as with all early studies. 2) Safety bloods, including urea and creatinine (with a calculated estimated glomerular filtration rate) will be taken at regular intervals highlighted in the Schedule of Assessments. 3) Scheduled urine assessments plus additional assessments may be performed if more than trace protein is found in the urine may be completed (including renal ultrasound, unscheduled microscopy and/or 24-hour urine collection; detection of blood or trace protein will not trigger microscopy in for females menstruating).
Hepatic System	1) No effect noted in human or nonclinical studies.	1) Extensive liver function testing will be completed including ALP, AST, ALT, GGT, Total protein as well as albumin and globulin, and coagulation will be measured as per the clinical Schedule of Assessments. 2) Specific eligibility criteria will be used to exclude participants with • Current or previous exposure to Hepatitis B and C • Bilirubin, ALT or AST consistently >ULN at Screening or Day -1. 3) Specific AR rules with regard to liver function test abnormalities will be implemented (please see Section 4.3). 4) Additional assessments could be added depending on clinical requirements, including an ultrasound ± fibro scan of the liver.
Cardiovascular system	1) No effects noted in human or nonclinical studies.	1) Standard monitoring as with all early phase studies 2) Comprehensive electrocardiogram (ECG) monitoring 3) Cardiac telemetry for 24 hours post-dose. 4) Strict Exclusion Criteria surrounding history of predisposing cardiac conditions (Section 5.4). A 24-hour Holter will be performed at Screening. This will be reported by a cardiac physiologist and reviewed by a cardiologist. It will allow the exclusion of participants with possibly confounding underlying cardiac conduction and rhythm abnormalities.
Respiratory System	1) No effects noted in human or nonclinical studies.	1) Standard monitoring as with all early phase studies

Target System	Effect	Risk Mitigation
Central nervous system	1) [redacted] Study 7266-CL-0001.	1) Standard monitoring as with all early phase studies 2) Participant welfare will continue to be monitored from signing of consent through to final follow up visit, with scheduled and, if necessary, unscheduled adverse event checks.
Haematological system	1) No effects noted in human or nonclinical studies.	1) Standard monitoring as with all early phase studies 2) Specific AR rules with regard to haematological test abnormalities will be implemented (please see Section 4.3).
Gastrointestinal system (including taste)	1) No effects noted in human or nonclinical studies.	1) Standard monitoring as with all early phase studies. 2) Regular biochemistry bloods for safety sampling.
Skin	1) There have been no reported injection site reactions reported in either nonclinical or clinical studies.	1) Scheduled site check monitoring and photography (see Schedule of Assessments). 2) Injection site reactions with a severity grading of moderate or above will be reported as an Adverse Event.
Reproductive and gynaeco-logical system	1) [redacted] 2) The effects of UPB-101 on fertility, pregnancy and lactation have not been investigated and remain unknown.	1) Specific contraceptive requirements will be in place for participants and will be used in inclusion criteria (see 5.5.1). 2) Female participants will need evidence of negative pregnancy tests during Screening and prior to dosing. 3) Participants who are pregnant or breastfeeding will be excluded. 4) Participant welfare will continue to be monitored from signing of consent through to final follow up visit, with scheduled and, if necessary, unscheduled Adverse Event checks.

Target System	Effect	Risk Mitigation
Immune system	1) [redacted]	1) Standard monitoring as with all early phase studies. 2) Participants will remain in unit until Day 15, in a clean and hygienic environment. This allows for close observation and reduces the risk of contracting an infection. 3) Participant welfare will continue to be monitored from signing of consent through to final follow up visit, with scheduled and, if necessary, unscheduled AE checks and safety assessments. 4) Participants with a history of any of the following will be excluded from the study: • Previous exposure or current infection with hepatitis B, hepatitis C or tuberculosis (TB). • HIV. • Evidence of active or suspected bacterial, viral, fungal or parasitic infections within the past 4 weeks prior to Screening. • History compatible with or diagnosis of a parasitic infection and has not been treated or has not responded to standard of care therapy.
	2) [redacted]	1) All clinical staff trained to diagnose and manage potential systemic inflammatory response. 2) The management algorithm for systemic inflammatory response will be included in the SOM. 3) UPB-101 will be administered in the in-house setting with close monitoring for reactions and a mandatory period of 'on the ward' supervision by ALS qualified staff for 4 hours post-dose, including assessment of vital signs, ECG, injection site reactions and adverse events.
	3) [redacted]	1) 12 weeks of immunogenicity follow up post-dose.

Target System	Effect	Risk Mitigation
	4) Allergic reaction	1) Participants with a history of significant allergic reaction or anaphylaxis to any substance will be excluded from this study. 2) All clinical staff trained to diagnose and manage potential allergic reaction. 3) UPB-101 will be administered in the in-patient setting with close monitoring for allergic reactions and a mandatory period of 'on the ward' supervision by ALS qualified staff for 4 hours post-dose, including assessment of vital signs, ECG, injection site reactions and adverse events.
Effects of a biologic compound	***1) PK*** The PK of biologics are well understood. They have a low volume of distribution, and do not undergo liver metabolism and therefore do not generate toxic metabolites.	1) Standard monitoring as with all early phase studies
Class effects (TSLPR inhibitor)	***1) Infection*** As a TSLPR inhibitor, UPB-101 has a theoretical increased risk of infection	1) Risk mitigation against class effects is described in the Immune System / Infection Risk section above

2. STUDY OBJECTIVES AND OUTCOMES

2.1 Objectives

2.1.1 Primary

- To characterize and compare the pharmacokinetics (PK) of single doses of UPB-101 in healthy Japanese and NJNEA adults.

2.1.2 Secondary

- To assess and compare the safety and tolerability of UPB-101 in healthy Japanese and NJNEA adults.
- To assess and compare the immunogenicity of UPB-101 when administered to Japanese and NJNEA adults.

2.1.3 Exploratory

- To assess the pharmacodynamic (PD) effect of UPB-101 on biomarkers related to inflammation, specifically the thymic stromal lymphopoietin (TSLP) pathway.

2.2 Endpoints

2.2.1 Primary

- Serum UPB-101 concentrations and analyses including C_{max}, t_{max}, AUC_{0-t} will be assessed. If appropriate, AUC_{0-inf}, $t_{1/2}$, apparent total body

clearance after dosing (CL/F), and apparent volume of distribution during the terminal elimination phase after dosing (Vz/F) will also be analyzed. These endpoints will be assessed from baseline through Day 85 ± 5 days in the PK Set.

2.2.2 Secondary

- The safety endpoints will include AEs, SAEs, physical examinations, clinical laboratory assessments, vital signs, electrocardiograms (ECGs) including telemetry, withdrawal of participants, and early terminations. These endpoints will be assessed from baseline through Day 85 ± 5 days in the Safety Set.
- The immunogenicity endpoint includes UPB-101 anti-drug antibodies (ADAs) and presence of neutralizing antibodies (Nabs). These endpoints will be assessed from baseline through Day 85 ± 5 days in the Immunogenicity Set.

2.2.3 Exploratory

- Specific PD biomarkers for exploratory analysis will be selected based on relevant data from ongoing clinical studies.

3. STUDY DESIGN

3.1 Overall study design

This is a randomized, open-label, parallel-group, pharmacokinetic study comparing the pharmacokinetics and safety of a single dose of UPB-101 in healthy Japanese and NJNEA adults. Japanese participants must have been born in Japan, with parents and grandparents born in Japan and lived for < 5 years outside of Japan.

Each participant will receive verbal and written information about the study, followed by signing of the Informed Consent Form (ICF) prior to any Screening procedures taking place. Following signing of the informed consent, participants will be evaluated for eligibility during the Screening Days -21 to -2. Participants who are eligible at the end of the Screening assessments will be admitted on Day -1 for confirmation of eligibility, then dosed on Day 1, and discharged on Day 15. All assessments performed during the study are detailed in the study Schedule of Assessments (Table 4 and Table 5). The study will be conducted at a single site in the UK.

Table 3: Planned treatment groups

Planned Treatment Groups	Participant Ethnicity (N Participants)	Treatment	Number of Injections to Achieve Dose	Number of Doses
1	Japanese (8)	UPB-101 [redacted] mg SC	[redacted]	Single dose
2	Japanese (8)	UPB-101 [redacted] mg SC	[redacted]	
3	Japanese (8)	UPB-101 [redacted] mg SC	[redacted]	
4	Non-Japanese Non-East Asian (8)	UPB-101 [redacted] mg SC	[redacted]	

The study consists of 4 treatment groups. Three (3) treatment groups will include Japanese healthy adult volunteers and 1 treatment group will include NJNEA healthy adult volunteers.

The 4 treatment groups will be assigned as few cohorts as operationally feasible to avoid period bias, and each cohort will attempt to contain at least two participants from each treatment group.

Each participant will receive one of the following dosing regimens in parallel:

- Treatment group 1 – 1 SC dose of [redacted] mg of UPB-101
- Treatment group 2 – 1 SC dose of [redacted] mg of UPB-101
- Treatment group 3 – 1 SC dose of [redacted] mg of UPB-101
- Treatment group 4 - 1 SC dose of [redacted] mg of UPB-101

Screening

Screening will commence with the informed consent process. After signing of the approved ICF, participants will be assigned a Screening number, and then undergo the scheduled Screening assessments to allow for assessment of safety and the study eligibility criteria. All women of childbearing potential (WOCBP) will undergo a serum beta human chorionic gonadotropin (β-HCG) pregnancy test. The assessments to be conducted on all treatment groups during the Screening Period (Day -21 to Day -2) are found in Schedule of Assessments (Table 4 and Table 5).

Admission

Participants who continue to meet the full enrolment criteria following review of all the results from Screening Day -21 to Day -2 will be admitted commencing their 'In-house' stay on Day -1. Safety assessments (including BMI, vital signs, triplicate ECGs, and safety clinical laboratory samples as well as a repeat β-HCG in WOCBP) will be performed to further evaluate the participant's eligibility.

Treatment

On Day 1 the final pre-dose safety assessments will be reviewed by a Research Physician and a final decision on each participant's study eligibility will be made. Following completion of these reviews, participants who remain eligible for enrolment will be randomly assigned to treatment group 1, 2, or 3 for Japanese participants, while NJNEA participants will be automatically allocated to treatment

group 4. Pre-dose, participants will undergo baseline safety assessments (including ECGs, vitals, laboratory assessments, as well as pre-dose PK and PD sampling. Participants will then receive subcutaneously the dose ([redacted], [redacted], or [redacted] mg) of UPB-101, depending on the treatment group to which they were assigned. After dosing, all participants will be closely monitored by medically qualified staff, including injection site checks, ECGs and vital signs as well as telemetry monitoring from at least 1 hour pre-dose until 24 hours post-dose. All participants will receive a meal at H4, followed by simultaneous ECG collection, as a means of confirming ECG data quality by observing shortening of QTc interval that is expected following a meal. Dosed participants will remain at the site through to Day 15 (inclusive) to ensure participant safety, accurate PK and PD sampling, and full study compliance. Participants will be discharged from the site on Day 15.

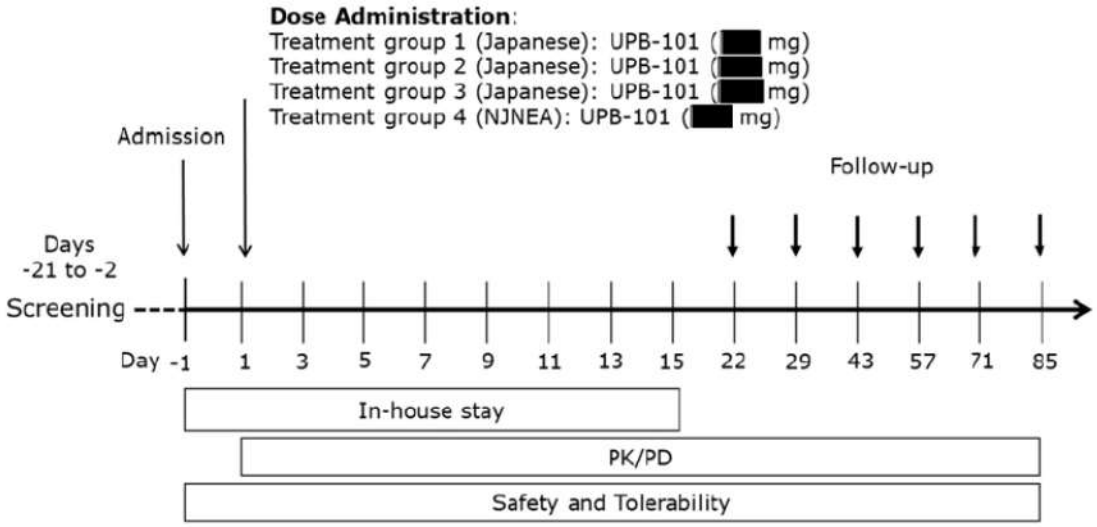
Follow-up

Participants will return for scheduled non-residential follow-up visits on Day 22, Day 29, Day 43, Day 57, and Day 71. During those visits participants will be checked for compliance of study restrictions and will undergo safety assessments (including safety laboratory samples, urinalysis and adverse event monitoring), as well as PK and PD sampling paired to ECG collection. A symptom-directed physical examination will be carried out at each visit, when indicated. The final scheduled visit is on Day 85 when participants will undergo final safety, PK, PD, and immunogenicity monitoring. As part of the safety assessments, all participants will undergo a second complete physical examination and all WOCBP will undergo serum β-HCG pregnancy test. WOCBP will be asked to inform the Investigator if they become pregnant between Day 85 and Day 120. Male participants with a WOCBP partner will be asked to inform the Investigator if their partner becomes pregnant between Day 85 and Day 120 post-dose. Participants who are WOCBP will be asked to perform a pregnancy test on Day 120 post-dose and report the result to the Investigator.

Participants who withdraw their consent before they have completed all study visits will be encouraged to undergo the Day 85/Final Visit procedures.

The study Schedule of Assessments (Table 4 and Table 5) details all assessments that will take place during the study. Some features may change in-line with the Adaptive Features (Table 6), including unscheduled safety visits.

Figure 3: Study flow chart



3.2 Schedule of Assessments

Table 4: Schedule of Assessments

Period	Screening	Admission	Treatment															Follow up					
Procedure	(D-21 to D-2)	D-1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D22	D29	D43	D57	D71	D85 / Final Visit
Informed consent [a]	X																						
Demographic data	X																						
Medical/Surgical history and prior medications	X	X[b]																					
Urine drugs of abuse screen (including urine cotinine)	X	X																X	X	X	X	X	X
Smoking history (pack/year) and current	X																						
Breath alcohol test	X	X																X	X	X	X	X	X
Serology (HIV 1 & 2, Hep B & C)	X																						
Pregnancy testing (females) [c]	X	X																	X		X		X
FSH (post-menopausal females) [c]	X																						
QuantiFERON®-TB Gold test	X																						
Inclusion/Exclusion criteria	X	X[b]																					
Study Residency		→																					
Check-in		X																					
Check-out																	X						
Non-residential visit	X																	X	X	X	X	X	X

Period	Screening	Admission	Treatment															Follow up					
Procedure	**(D-21 to D-2)**	**D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D13**	**D14**	**D15**	**D22**	**D29**	**D43**	**D57**	**D71**	**D85 / Final Visit**
Randomization for treatment groups 1 to 3			X																				
Study drug administration [d]			X																				
Meals [e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Safety and tolerability:																							
AE recording/concomitant medication [f]		→																					
24h Holter ECG [g]	X																						
Telemetry [h]			X	X																			
Vital signs [i]	X	X	X	X		X			X						X		X	X	X	X	X	X	X
12-lead ECG [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight/height/BMI [k]	X	X[k]																					
Physical examination [l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Haematology/Biochemistry /Coagulation [m]	X	X	X						X						X		X		X		X		X
Urinalysis	X	X							X						X				X		X		X
COVID-19 testing [n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess injection site reactions [o]			X	X																			

Period	Screening	Admission	Treatment															Follow up					
Procedure	**(D-21 to D-2)**	**D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D13**	**D14**	**D15**	**D22**	**D29**	**D43**	**D57**	**D71**	**D85 / Final Visit**
PK/PD/Immunogenicity assessments																							
PK blood sampling [p]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD blood sampling [q]			X	X	X	X	X	X	X	X							X	X	X	X	X	X	X
Serum ADA and Nabs (immunogenicity)			X[r]																X				X

a) Procedures will not occur until informed consent is completed. Consent outside of the defined Screening window (D-21 to D-2) is allowed.
b) Update only.
c) Serum pregnancy testing is to be performed at Screening, Day -1 and Day 85 for WOCBP. At other visits, a urine pregnancy test is performed. All post-menopausal females will require an FSH serum test at Screening to confirm post-menopausal status.
d) Study drug will be administered as a single dose on Day 1 via SC injection, according to the randomization schedule.
e) On Day 1, breakfast will not be served. Lunch will be served after completion of H4 procedures. Dinner and snack will be served after completion of H8 procedures and at H12, respectively. Standard meals will be served at standard unit times from Day 2 to Day 14. On Day 15 (dismissal day), breakfast will be optional.
f) AEs and concomitant medications will be collected at each visit from the time of consent until the end of study visit, and daily during study residency.
g) A Holter ECG assessment must be performed at Screening to exclude pre-existing ECG abnormalities.
h) Continuous 12-lead telemetry will be recorded from at least 1-hour pre-dose to 24 hours post-dose
i) Vital signs (respiratory rate, tympanic temperature, blood pressure and heart rate) will be measured after at least 5 minutes rest in supine position, according to the timepoints in Table 5.
j) 12-lead ECGs (triplicate) will be measured after at least 10 minutes rest in supine position, according to the detailed timepoints in Table 5.
k) Height will be measured at Screening only.
l) A Full Physical examination will be carried out at Screening and Day 85. Symptom-directed physical examinations will be performed at all other time-points.
m) Pre-dose on Day 1. Additional unscheduled safety blood samples may be added at the investigator's discretion.
n) COVID-19 testing will be carried out as per the site's latest COVID-19 Infection Control Guidelines and pre-entry algorithms.
o) Injection site evaluations will be performed at pre-dose, 30 mins, 1-hour, 4-hour, 12-hour and 24-hour post-dose. Additional examinations may be performed as 'unscheduled' assessments, as required, until resolution of symptoms. Injection site photos will be taken at the same timepoints to monitor any changes.
p) Pre-dose, 4-hour post-dose and 8-hour post-dose on Day 1; time matched to dosing at all other time points. All PK sampling beyond Day 1 will be collected alongside a valid triplicate ECG
q) Pre-dose on Day 1; time matched to dosing at all other time points.
r) Pre-dose.

Table 5 Schedule of Assessments with detailed timepoints for 12-lead ECGs, vital signs, PK and PD samples

Study Day	Time (hours)	PK sampling (serum)	PD sampling (plasma)	Vital signs [a]	12-lead ECG [b]
D1	-2				X
	-1			X	X
	-0.5	X	X		X
	0.5			X	X
	1			X	X
	4	X		X	X
	5				X
	6				X
	7				X
	8	X			X
D2	24	X	X	X	X
D3	48	X	X		X
D4	72	X	X	X	X
D5	96	X	X		X
D6	120	X	X		X
D7	144	X	X	X	X
D8	168	X	X		X
D9	192	X			X
D10	216	X			X
D11	240	X			X
D12	264	X			X
D13	288	X		X	X
D14	312	X			X
D15	336	X	X	X	X
D22	504	X	X	X	X
D29	672	X	X	X	X

Study Day	Time (hours)	PK sampling (serum)	PD sampling (plasma)	Vital signs [a]	12-lead ECG [b]
D43	1008	X	X	X	X
D57	1344	X	X	X	X
D71	1680	X	X	X	X
D85	2016	X	X	X	X

a) Vital signs (respiratory rate, tympanic temperature, blood pressure and heart rate) will be measured after at least 5 minutes rest in supine position.
b) 12-lead ECGs (triplicate) will be measured after at least 10 minutes rest in supine position. ECGs will be time matched to occur before PK/PD blood sampling. ECGs collected on Day 22, Day 43, Day 57 and Day 71 will be collected for safety purposes only and will be reviewed by the Investigator. ECG data from these timepoints will be transferred and stored at the central ECG laboratory but will not be adjudicated unless requested by the Sponsor. ECGs collected on all other timepoints will be reviewed by the Investigator but will also be transferred and adjudicated by the central ECG laboratory. The outcome of the adjudication will be reported in the Clinical Study Report (CSR).

3.3 Order of procedures, meals, scheduling time windows and protocol deviations

Order of Procedures / Priorities:

When the protocol's Schedule of Assessments requires that multiple procedures occur at the same timepoint, PK blood sampling takes priority and is to be scheduled at the exact time point defined in the Schedule of Assessments.

There is no set order of procedures at Screening, Admission or during Follow-Up. During the In-house Period, the order of procedures should be ECG, Vital Signs, Blood Samples including PK/PD, and Meal. Should there be any delay to procedures, PK/PD assessments timings should be prioritized above order of procedures.

Meals:

Meals will be provided in the order below on Day -1 and the dosing day (Day 1), following the standard timings of the research unit:

- Lunch (at least 4 hours post-dose)
- Dinner (8 hours post-dose)
- Snack (12 hours post-dose).

Meals for the non-dosing residential days will be served as below, following the standard timings of the research unit:

- Breakfast (following the morning procedures)
- Lunch
- Dinner
- Snack

Scheduling time windows:

The permitted time windows are set out in the Data Handling Protocol for scheduling time windows (DHP STW) and factored into the design of the Master Treatment Schedule (MTS).

Protocol deviations:

Where the time of clinical assessment deviates from the scheduling time window in the DHP STW, this will be considered a protocol deviation. These deviations will be identified, classified (minor, major, critical), and managed in accordance with the DHP STW.

3.4 Adaptive design

This study incorporates the use of an adaptive design. Study specific adaptive features and their limits are described in Table 6.

Adaptive features may be implemented only with the approval of the Sponsor. Implementation of adaptive features affecting whole treatment, or the entire study, will be documented in a non-substantial amendment.

The exceptions to this are those adaptive features in Table 6 that relate to individual participant safety. These may be implemented at the discretion of the Investigator and recorded in that participant's source data.

Table 6: Adaptive protocol features

Adaptive Study Design Areas	Features	Limits
Replacement of withdrawn participants	1. Withdrawn participants can be replaced at the discretion of the Sponsor and the Investigator. The replacement participant(s) will be enrolled into the same treatment group as the original participant(s). Evaluable data from the withdrawn participant will be included in the analysis as appropriate. 2. Replacement participants may be enrolled in an ongoing treatment group, dosed together as a group or dosed separately.	I. Study-specific AR rules apply (section 4.3)

Adaptive Study Design Areas	Features	Limits
Samples and Assessments (safety)	1. Additional safety assessments may be performed on an individual participant if it is considered clinically necessary by the Investigator for individuals on a case-by-case basis. 2. Additional safety assessments (including but not limited to laboratory safety samples, vital signs and ECGs) may be added to the Schedule of Assessments at additional time-points for an upcoming treatment group if necessary from a safety/tolerability perspective, on the basis of evolving data. 3. Additional safety assessments may refer to either: a. an increased number of the same safety assessments planned in the existing Schedule of Assessments. b. additional parameters (specific tests) on assessments already scheduled e.g., troponin tests on safety blood samples. c. additional safety tests requiring additional blood/urine sample collections or other clinical procedures e.g., ultrasound scans. 4. Specialist referrals (e.g., to a cardiologist) may be made (and may include all relevant assessments and investigations) if it is considered clinically necessary by the Principal Investigator (PI), Sponsor or Safety Review Committee (SRC) for individuals on a case-by-case basis. 5. The timing of safety assessments including but not limited to laboratory safety samples, vital signs and ECGs may be adjusted in accordance with evolving data and dosing schedule.	I. The maximum blood volume for scheduled assessments is given in Section 7.14. This maximum may only be exceeded if additional unscheduled blood samples/ investigations are performed as necessary to ensure the safety of the individual participants. II. If additional time points for safety assessments are required for upcoming participants in specified treatment groups, this will be documented in a non-substantial amendment, providing the overall risk profile of UPB-101 has not changed. III. If additional safety assessments or parameters are required for upcoming participants in specified treatment groups and have a similar risk profile to those planned in this study protocol, they will be documented in a non-substantial amendment. Additional safety assessments required for upcoming participants in specified treatment groups that are more invasive or have a different risk profile to those in this current protocol must be detailed in a substantial amendment. IV. If there are no clinically significant findings in safety assessments up to Day 85, further follow-up can be discontinued. V. A maximum number of specialist referrals for individuals will be determined on a case-by-case basis and cannot be pre-defined as investigations will be performed as necessary to ensure the safety of the individual participants.

Adaptive Study Design Areas	Features	Limits
Samples and assessments (PK)	1. Samples will be collected at timepoints detailed in the Schedule of Assessments and will be processed and stored as detailed in the Laboratory Manual.	I. Follow Schedule of Assessments and max blood volume will not be exceeded. II. Analysis of PK samples taken between Day 9 and Day 14 is optional at the Sponsor's discretion (which may or may not be reported as part of this study).
Samples and assessments (PD)	1. Specific PD biomarkers for exploratory analysis will be selected based on relevant data from ongoing clinical studies.	I. Follow Schedule of Assessments and max blood volume will not be exceeded.
In-house duration and visit numbers	1. The in-house stay or follow-up period may be prolonged if: a. it is considered clinically necessary to prolong the in-house stay by the PI/delegate for individuals on a case-by-case basis b. the SRC considers it necessary from a safety/tolerability point 2. The follow-up period for a dose treatment group may be prolonged if evolving safety and tolerability data requires a longer or shorter follow-up period.	I. A maximum extended in-house or follow-up period cannot be pre-defined as the extension will be as long as necessary to ensure the safety of the individual participant(s). II. The maximum extended in-house or follow-up period for study treatment groups will be based on evolving safety, tolerability and PK data and will not usually exceed 5x human $t_{1/2}$ of UPB-101. III. Alterations in duration of in-house stay or follow-up need to ensure that sufficient data are obtained to fulfil the study objectives and be a reflection of the established safety and tolerability PK profile
Screening	1. Screening assessments, including Holter ECG recordings, performed at Richmond Pharmacology Ltd (RPL) on participants screened (but not randomized) for another study can be used for this study to avoid unnecessary tests. 2. Screening assessments performed prior to signing the ICF for this study at RPL on volunteers screened (but not randomized) for another study or screening for a generic protocol can be used for this study to avoid unnecessary tests/repeats.	I. The assessments must meet protocol criteria (e.g., the method to be used). II. The assessments (except Holter ECG recordings) must be performed within the protocol defined Screening window (Day -21 to -2. III. Holter ECG recordings performed either under this or another approved clinical study protocol and informed consent are valid for a period of three months before Day -2.

Adaptive Study Design Areas	Features	Limits
ECG analysis	1. All ECGs will be assessed for safety by the Investigator and will be transferred to the central ECG laboratory. 2. ECGs from timepoints on Day 22, Day 43, Day 57 and Day 71 will be stored at the central ECG laboratory but not adjudicated unless requested by the Sponsor. 3. ECGs from all other timepoints will be adjudicated and the output from the adjudication will be included in the CSR.	I. There will be comprehensive collection of ECGs (in triplicate), time matched to PK assessments, throughout the study. II. If a safety issue occurs that necessitates the adjudication of ECG data from the timepoints listed in (Features no. 2), this analysis will be performed and will be reported in the CSR. III. If adjudication of ECGs from the timepoints listed in (Features no. 2) is requested by the Sponsor for another reason, this analysis will be performed and may or may not be reported in the CSR.
Post-dose telemetry	1. Continuous 12-lead telemetry will be monitored and recorded from at least 1-hour pre-dose to 24 hours post-dose	I. Post-dose telemetry data will be stored and can be optionally analyzed and reviewed by cardiologist in case of clinically significant AE and/or be used to provide additional information for more extensive optional cardiac assessments, or in any other circumstances where analysis may be beneficial. II. The results of assessments performed in case of a clinically significant AE will be reported in the CSR. The results of any other optional assessments may or may not be reported as part of this study.

3.5 Rationale for study design and dose of UPB-101

This study is designed for the purpose to increase understanding of the clinical profile of UPB-101.

The rationale for investigating a possible difference in the PK of UPB-101 attributable to the Japanese ethnicity is to determine the optimal dose and dosing frequency of UPB-101 in this specific population, which due to genetic differences may be different to that of other ethnicities. 24 Japanese participants (8 participants across 3 treatment groups) and 8 NJNAE participants is sufficient to explore this objective. The NJNEA treatment group will aim to include Caucasian and 2-3 non-Caucasian participants to ensure diversity. They must also be 'non-East-Asian' (i.e., not Chinese, Korean, Mongolian or Taiwanese), as there may be genetic overlap between Japanese and East-Asian participants.

The study will be open label.

Nonclinical and clinical studies have shown no safety concerns for UPB-101 administered in doses significantly higher than the maximum planned dose for this study ([redacted] mg). Therefore, sentinel or ascending dosing is not required. There are also no adaptive features which allow for doses that exceed the maximum planned dose of [redacted] mg, which is well within the safe range of doses already tolerated in the FIH study. As a result, there are no dose escalation rules or dosing decisions to be made between cohorts; therefore, there is no need for an interim SRC review.

All treatment groups will enrol and dose in parallel. On Day 1, Japanese members of the cohort will be randomized to either treatment group 1, 2 or 3, and NJNEA participants will automatically be assigned to treatment group 4. The study will be completed in as few cohorts as operationally possible to minimize period bias. Attempts will be made to include in each cohort at least 2 participants assigned to each of the 4 treatment groups (therefore a minimum of 8 participants per cohort and a maximum of 4 cohorts to complete the study).

Safety will be monitored on an on-going basis by the investigator and medical monitor including vital signs, laboratory and urine tests, physical examination, AEs and injection site monitoring. The predicted exposures for the highest planned dose ([redacted] mg) are comfortably below those already found to be safe and well-tolerated in humans; therefore, there are no anticipated ADRs or clinical laboratory abnormalities. At the Investigator and Sponsor discretion, any safety concerns identified during the study may result in suspension of enrolment at that dose level pending safety review and outcome of an *ad hoc* SRC (Section 4.2). Dosing at lower levels may continue, if permitted in line with the study specific AR rules (Section 4.3). Should the clinical study be suspended because of any safety concern, 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).

The safety, tolerability, PK, and immunogenicity of a single ascending dose in NJNEA adults have already been characterized in clinical study 7266-CL-0001. Safety, tolerability, immunogenicity and PK assessments will be conducted at specified intervals during this study which bracket the $t_{1/2}$ (median = [redacted] days) and time to maximum concentration (t_{max}) ([redacted]) observed in study 7266-CL-0001 for a single dose of [redacted] mg/kg UPB-101 administered subcutaneously.

3.5.1 Justification for the selected dose level

In the nonclinical 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 guideline (FDA 2005)). Thus, the highest dose of [redacted] mg to be used in this study is 7.5-fold lower than the HED NOAEL dose determined in nonclinical 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) and as a single SC dose of [redacted] mg ([redacted] mg/kg; assuming a 70 kg human) to healthy male and female non-Japanese participants and was 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_{0-inf}) and C_{max} in that study

increased dose proportionally. At the highest dose tested ([redacted] mg/kg), C_{max} and $AUC_{0\text{-}inf}$ after a single IV administration were [redacted] µg/mL and [redacted] days·µg/mL, respectively. Bioavailability after SC administration was [redacted]. 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).

The proposed study will explore SC doses in the [redacted] mg range. These doses are all significantly below the maximum dose ([redacted] mg/kg IV) administered in the completed SAD study (above and Section 1.1) and there is a significant margin of safety with regard to exposure at doses which have previously been shown to be safe and well-tolerated.

Table 7 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 $AUC_{0\text{-}inf}$ for a single SC injection in this study (at the highest dose of [redacted] mg SC) are [redacted] and [redacted], respectively, when compared with the observed C_{max} and $AUC_{0\text{-}inf}$ following administration of [redacted] mg/kg IV in Study 7266-CL-0001, a dose that was found to be safe and well tolerated.

This data provides the rationale for the randomized treatment group design. For all treatment groups, 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 7: 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)	$AUC_{0\text{-}inf}$ (days·µg/mL)	C_{max} IV/ C_{max} SC	$AUC_{0\text{-}inf}$ IV/ $AUC_{0\text{-}inf}$ SC
SC	[redacted]					
SC						
SC						
SC						
IV						

Abbreviations: $AUC_{0\text{-}inf}$=area under the concentration-time curve from the time of dosing extrapolated to time infinity; C_{max}=maximum observed serum concentration; IV=intravenous; PK=pharmacokinetic; SAD=single ascending dose; SC=subcutaneous.

The doses selected for this study (i.e., [redacted] mg, [redacted] mg, and [redacted] mg) were informed by the PK and PK/PD data derived from the SAD study in healthy adult male and female volunteers. All three doses resulted in serum concentrations of UPB-101 that remained above the therapeutic threshold ([redacted] for at least [redacted] and are, therefore, candidates for future drug development.

Consequently, these same three doses are being administered to asthmatic participants in the ongoing MAD study. The results from this Japanese ethno-bridging study and the MAD study will help determine the optimal dose and dosing frequency (based on safety, tolerability, PD, immunogenicity, and PK) to be applied to future clinical studies.

3.5.2 Precautions to be applied for dosing of different treatment groups

All treatment groups will enrol in parallel. A human study has already been completed at significantly higher dose levels with no safety concerns identified. Should a safety concern arise an *ad hoc* SRC will be arranged. In addition, study AR/stopping rules are in place for the duration of the study.

The anticipated exposure after the highest dose of [redacted] mg is expected to be [redacted] times less than the correspondent NOAEL exposure in animals and humans.

3.5.3 Monitoring and communication of adverse events/reactions

AEs will be continuously monitored throughout the study from the signing of the ICF until the last follow-up assessment. Each AE reported will be assessed by a trained Research Physician (RP) who will ensure that the event is dealt with appropriately, based on clinical findings, study protocol, study operations manual and Richmond Pharmacology Limited (RPL) Standard Operating Procedures (SOPs). AEs will be documented in the participants' source Case Report Forms (CRFs).

The collection, evaluation and reporting of adverse events/reactions arising from this clinical study will be performed in accordance with:

- "Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') (2011/C 172/01)".
- International Council for Harmonization (ICH) guideline E2F "Note for guidance on development safety update reports (DSUR)".
- International Council for Harmonization (ICH) guideline E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting".

If any information relating to the IMP in this study becomes available after the submission of a final protocol to the Competent Authority which may impact on the conduct of the study, including but not limited to the risk and benefit evaluations underpinning approvals and participant's consent, Upstream Bio shall notify RPL in writing as soon as practically possible and the parties will agree, in writing, what steps need to be taken if any.

3.5.4 Investigator site facilities and personnel

This study will be conducted in a specialized early phase Clinical Pharmacology Unit with on-site resuscitation equipment and medication, in addition to access to an acute hospital with critical care facilities, thus ensuring direct access to equipment and staff for resuscitating and stabilizing participants in acute medical conditions and emergencies. The study is conducted by an experienced PI and well-trained medical and technical staff with ample experience in the conduct of early phase clinical studies.

The study is designed to closely monitor, treat and communicate potential expected adverse reactions as well as potential unexpected adverse events.

4. DECISION-MAKING, RULES AND LIMITS

4.1 Rules and limits governing decision-making

The criteria and rules that will govern Investigator decisions are:

1. AE stopping rules (Table 9 and Table 10)
2. Adaptive features and their limits (Table 6).

4.2 Safety Review Committee

There are no SRC meetings scheduled during the study. Results of the SAD study performed with UPB-101 or placebo were reported in Section 1. In that clinical study, UPB-101 was safe and well-tolerated. The highest dose administered was [redacted] mg/kg (the equivalent of approximately [redacted] mg), while the highest proposed dose of UPB-101 in his study is more than [redacted] lower ([redacted] mg). The predicted exposure levels for the highest planned dose in this study are [redacted] than those that were safe and well tolerated in the SAD study.

However, if required due to Investigator or Sponsor safety concerns or reaching of a dose-limiting AR stopping rule necessitating an *ad hoc* SRC, it will consist of, as a minimum:

- RPL Principal Investigator or delegate
- Upstream Bio Medical Monitor or delegate

Further internal or external experts such as a pharmacokineticist, and/or a statistician, may be consulted by the SRC as necessary. Any additional information, if required will be included in the SOM.

They will review the required data in accordance with Table 8, Table 9, and Table 10. The safety data to be reviewed will include listings of TEAEs, clinically significant vital signs, physical examinations, ECGs, clinical laboratory results, and available PK data, as well as participant disposition.

4.3 Adverse reaction (AR) rules

An AR is any AE where there is a reasonable possibility of it being related to the IMP(s). ARs will be classified in accordance with Sections 8.1 and 8.3 to support standardized recording and reporting.

- Seriousness will be assessed using the criteria in Section 8.1.
- Severity and causality will be assessed using the criteria in Section 8.3.

Seriousness and severity are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves to define and trigger regulatory reporting obligations.

Seriousness and severity grade both have consequences when applying AR rules. Seriousness of an AR always overrides the severity grade and the rules for Serious AR should be applied, irrespective of severity grade.

These rules will only apply to treatment-emergent AEs/SAEs where there is a reasonable possibility of relationship to the IMP (i.e., ARs and SARs). Every AE will be assessed in the following order:

1) the impact on the individual participant

2) the impact on the treatment group (and higher dose treatment groups)
3) the impact on continuation or suspension of the overall study.

Dose-limiting ARs are specific ARs that for the purposes of this study, depending on their severity grading, the frequency at which they occur and their 'seriousness', will result in either:

1) Suspension of dosing at the same or higher dose or
2) Suspension of dosing of all dose/treatment groups (i.e., whole study suspension).

This is a single-dose study and therefore individual AR rules are not applicable. However, if a participant displays immediate signs of an AR whilst UPB-101 is being administered, study drug administration will be immediately abandoned, and the participant will be reviewed and managed in line with current clinical guidelines.

Table 8 shows the definition of the dose-limiting ARs for this study.

Table 8: Dose-limiting adverse reactions

Severe	Serious
Haematological Adverse Reaction Grading	
• Hb drop of >25% from baseline on Day -1 (only for values below the laboratory reference range). • Platelet count drop of >25% from baseline on Day-1 (only for values outside the laboratory reference range), or absolute value of <80 x10^9/L. • Clinically significant neutrophil drop[a] • Any other haematological toxicity which in the opinion of the Investigator would preclude further dosing of participants at this dose level or higher	
Liver Adverse Reaction Grading	
• ALT or AST value >3 x and <5 x ULN • ALT or AST value >3 x and <5 × ULN and symptomatic[b] **OR** ALT or AST value >5× ULN +/- symptoms[b]	• Potential drug-induced liver injury (DILI), as defined by ALT or AST value >3 × ULN together with bilirubin >2 x ULN.
Cardiac Adverse Reaction Grading	
• QT interval prolongation: A prolongation of the uncorrected QT interval of greater than 500 ms, using consistent, technically valid triplicate ECG.	
Injection Site Reaction Grading	
• Ulceration or necrosis • Severe tissue damage • Operative intervention indicated	

Severe	Serious
Other Adverse Reaction Grading (Global Clinical Assessment)	
Overall clinical condition is asymptomatic or is symptomatic with one or more of the following characteristics: • Significant impact on usual self-care activities • Inability to perform usual social and functional activities • The deviation from reference range for the population and from the participant's baseline has significant clinical impact, it is acute safety concern or unanticipated risk and requires close and continuous monitoring • The reversibility of the condition to baseline condition takes significantly longer than desirable or anticipated, with significant impact on the participant's wellbeing • Intervention or treatment essential to treat the acute manifestations and to prevent worsening.	• Any AR that meets seriousness criteria (i.e., an SAE).

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ECG=electrocardiogram; Hb=haemoglobin; ULN=upper limit of normal
[a] Clinically significant being defined as requiring of additional investigation or treatment to manage the finding.
[b] Symptoms or signs include fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (eosinophil percent or count above the ULN).

The treatment group and study Stopping Rules for dose-limiting ARs are described in Table 9 and Table 10 respectively.

Table 9: Treatment group stopping rules

	Frequency of dose-limiting ARs	
Action	**Severe**	**Serious**
Dosing of remainder of treatment group (and all other treatment groups of the same or higher dose) to be suspended[a] while dosing of lower dose treatment groups may continue	≥2	≥1 deemed at least possibly related to the study drug

[a] Continuation of dosing requires regulatory approval via a substantial amendment.

Table 10: Study stopping rules

	Frequency of dose-limiting ARs	
Action	**Severe**	**Serious**
All dosing suspended[a]		≥1 where SAE deemed at least possibly related to the study drug and is either life threatening or leads to death

[a] Continuation of dosing requires regulatory approval via a substantial amendment.

5. SELECTION AND WITHDRAWAL OF PARTICIPANTS

5.1 Number and source of participants

Approximately 32 participants will be recruited to this study in total (approximately 24 Japanese and 8 NJNEA healthy adult male and female participants). Japanese participants will be randomized to treatment groups 1-3, NJNEA participants will be allocated to group 4.

- Treatment group 1 (Japanese N=8): UPB-101 [redacted] mg
- Treatment group 2 (Japanese N=8): UPB-101 [redacted] mg
- Treatment group 3 (Japanese N=8): UPB-101 [redacted] mg
- Treatment group 4 (NJNEA N=8): UPB-101 [redacted] mg

5.2 Replacement participants

Additional participants may be recruited to replace any withdrawn participants, in order to ensure that 32 participants complete the study. Replacement participants may be enrolled as described in Table 6 – Adaptive protocol features.

5.3 Inclusion criteria

Participants must meet all of the following criteria to be eligible for enrolment in this study:

1. Ability to provide written, personally signed, and dated informed consent to participate in the study, in accordance with the ICH Good Clinical Practice (GCP) Guideline E6 (R2) (2016) and applicable regulations, before completing any study-related procedures.
2. An understanding, ability, and willingness to fully comply with study procedures and restrictions.
3. Male or female, aged ≥18 to ≤40 years at the date of signing informed consent.
4. Participants must have a BMI between 18.0 kg/m² - 25.0 kg/m² (inclusive) at Screening and Day -1.
5. For Japanese (treatment groups 1, 2 and 3), participants must be:
    a. Born in Japan, holding a Japanese passport,

b. Not living outside Japan for more than 5 years at the date of signing informed consent,
c. Have all 4 grandparents Japanese.

For NJNEA treatment group 4, participants must be:

d. Non-Japanese
e. Non-East Asian (Chinese, Korean, Mongolian or Taiwanese).

6. Healthy as defined by:
    a. The absence of clinically significant illness and surgery within 4 weeks prior to dosing.
    b. The absence of clinically significant history of neurological, endocrine, cardiovascular, respiratory, haematological, immunological, psychiatric, gastrointestinal, renal, hepatic, and metabolic disease.

    As assessed by the Investigator, and that may confound the results of the study, pose an additional risk to the participant by study participation or affect the action, absorption, or disposition of UPB-101.
7. Satisfactory medical assessment with no clinically significant or relevant abnormalities as determined by medical history, physical examination, vital signs, 12-lead ECG and clinical laboratory evaluation (haematology, biochemistry, coagulation, and urinalysis) that could interfere with the participant's participation in or ability to complete the study as assessed by the Investigator.
8. Participants must agree to following the highly effective contraceptive requirements for the applicable duration, as described in Section 5.5.1.
9. Participants must agree not to donate sperm or ova from the time of the administration of study medication until 120 days later.

5.4 Exclusion criteria

Participants will be excluded from enrolment in this study if they meet any of the following criteria:

1. Participant has evidence of active proven or suspected bacterial, viral (including COVID-19), fungal or parasitic infections within the past 4 weeks prior to Screening (e.g., sinusitis, common cold, viral syndrome, flu-like symptoms).
2. Participant 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.
3. Participant has a history of malignancy of any type, other than treated *in situ* cervical cancer or surgically excised non-melanomatous skin cancers, within 5 years before Screening.
4. History of significant allergic reaction (anaphylaxis, angioedema) to any product (food, pharmaceutical, etc).

5. The history or presence of any of the following cardiac conditions: known structural cardiac abnormalities; family history of long QT syndrome; cardiac syncope or recurrent, idiopathic syncope; exercise-related clinically significant cardiac events.

6. Any clinically significant abnormalities in rhythm, conduction or morphology of resting ECG or clinically important abnormalities that may interfere with the interpretation of QTc interval changes. This includes participants with any of the following (at Screening or Day -1):

   - Sinus node dysfunction.
   - Clinically significant PR (PQ) interval prolongation.
   - Intermittent second- or third-degree AV block.
   - Complete bundle branch block.
   - Sustained cardiac arrhythmias including (but not limited to) atrial fibrillation or supraventricular tachycardia; any symptomatic arrhythmia with the exception of isolated extra systoles.
   - Abnormal T wave morphology which may impact on the QT/QTc assessment.
   - QT interval corrected using the Fridericia's formula (QTcF) > 450 ms (males and females).
   - Any other ECG abnormalities in the standard 12-lead ECG and 24-hour 12-lead Holter ECG or an equivalent assessment which in the opinion of the Investigator will interfere with the ECG analysis, including pacemakers.

   Participants with borderline abnormalities may be included at the discretion of the PI (if the deviations are considered not to be clinically significant or their inclusion in the study does not pose a risk to the participant's health or the integrity of the study).

7. Has vital signs consistently outside of the following normal range at Screening or Day -1. Acceptable normal range is as follows:

   - supine HR 40 - 90 bpm (after at least five minutes of supine rest)
   - supine blood pressure (after at least five minutes of supine rest):

     systolic blood pressure: 90 - 130 mmHg

     diastolic blood pressure: 40 - 90 mmHg

8. Positive test for Hepatitis B surface antigen (HBsAg and/or Hep B core), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at Screening or has a positive QuantiFERON® tuberculosis Gold (QFT-G) test for tuberculosis at Screening. Participants with an indeterminate QFT-G test may be re-tested; if a re-test remains indeterminant or is positive, the Participant will be excluded.

9. Has Total Bilirubin, ALT or AST consistently > ULN at Screening or Day -1 (up to two repeats may be taken; participant may be included if two out of the three total results are ≤ ULN).

10. Participant has an estimated glomerular filtration rate (eGFR) of <80 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration equation at Screening or Day -1 (up to two repeats may be taken; participant may be included if 2 out of the 3 total results are ≥80 mL/min/1.73 m^2.

11. Any other abnormal findings on vital signs, ECG, physical examination or laboratory evaluation of blood and urine samples that the Investigator judges as likely to interfere with the study or pose an additional risk in participating.

12. Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participant at risk because of participation in the study may influence the result of the study, or the participant's ability to participate in the study.

13. Female participants who are pregnant (including a positive serum pregnancy test at Screening or on Day -1) or breastfeeding.

14. Positive test results for alcohol or drugs of abuse (including cotinine) at Screening or Day -1.

15. History or clinical evidence of substance and/or alcohol abuse within the 2 years before Screening. Alcohol abuse is defined as regular weekly intake of more than 14 units (for both males and females), using the following NHS alcohol tracker https://www.nhs.uk/oneyou/for-your-body/drink-less/know-your-alcohol-units/

16. Use of tobacco in any form (e.g., smoking or chewing) or other nicotine-containing products in any form (e.g., gum, patch, electronic cigarettes) within 3 months prior to the planned first day of dosing.

17. Has used any of the following:

    a. prescription medication (excluding female hormonal contraception or replacement therapy) within 14 days or 5 half-lives of the drug (whichever is longer), OR

    b. over-the-counter medication (including multivitamin, herbal, or homeopathic preparations; excluding paracetamol - up to 2g paracetamol per day permitted) during the 7 days or 5 half-lives of the drug (whichever is longer), OR

    c. Consumption of herbal remedies or dietary supplements containing St. John's Wort during the 3 weeks prior to Day 1, that the Investigator judges is likely to interfere with the study or pose an additional risk in participating.

18. Participants who have received or are planning on receiving a vaccination (including COVID-19) within 4 weeks prior to Day 1.
19. Previous exposure to UPB-101, or known or suspected intolerance or hypersensitivity to UPB-101, any closely related compound, or any of the stated ingredients.
20. Treatment with an investigational drug within 90 days or 5 half-lives preceding the first dose of study medication (or as determined by the local requirement, whichever is the longer).
21. Participant has received an antibody or therapeutic biologic product during the 6 months prior to planned date of study administration.
22. Donation of blood or blood products within 90 days prior to study medication administration, or experienced loss of blood ≥500 mL within 8 weeks of Screening.
23. Has a mental incapacity or language barriers precluding adequate understanding, co-operation, and compliance with the study requirements.
24. An inability to follow a standardized diet and meal schedule, as required during the study.
25. Participants with veins on either arm that are unsuitable for intravenous puncture or cannulation (e.g., veins that are difficult to locate, or a tendency to rupture during puncture).
26. Prior screen failure (where the cause of the screen failure is not deemed to be temporary), randomization, participation, or enrolment in this study. Participants who initially failed due to temporary non-medically significant issues are eligible for re-screening once the cause has resolved.

5.5 Participant restrictions

Participants will have to comply with the restrictions described in Table 11. Participants must also comply with the latest COVID-19 safety measures/ testing applicable at the site at that time, for entry into the unit and during in-house stays.

Table 11: Participant restrictions

Items participants must not consume or do	When participants must stop	When participants can re-start
Tobacco in any form (e.g., smoking or chewing) or other nicotine-containing products in any form (e.g., gum, patch, electronic cigarettes)	From three months prior to the planned first day of dosing.	After study completion/last visit.
Meals/snacks/water	Whenever participants are confined in the ward, only the drinks and meals provided by	After discharge from the unit.

Items participants must not consume or do	When participants must stop	When participants can re-start
	the study personnel will be allowed. Standard meals will be provided at the standard unit times as stated in the study schedule, and meals should be completed each time.	
Caffeine-containing or Xanthine-containing products	48 hours before the planned study drug administration and each out-patient/ follow-up visit.	After study completion/last visit.
Energy drinks or drinks containing taurine, glucuronolactone (e.g., Red Bull)	48 hours before the planned study drug administration and each out-patient/ follow-up visit.	After study completion/last visit.
Alcohol	48 hours before the planned study drug administration and each out-patient/ follow-up visit.	After study completion/last visit.
Strenuous physical activity	48 hours before Screening, admission and out-patient/follow-up visit. Participants should not start new physical training activities during the study.	After study completion/last visit.
Any prescription medication. For details, including exceptions see Section 5.4 Exclusion Criteria, and Section 6.3 Concomitant Medications.	14 days or 5 half-lives (whichever is longer) before the planned study drug administration.	After study completion/last visit. If participants have a medical need to take any medication or have any medications prescribed to them by a doctor, they should follow the medical advice but inform the Investigator as soon as possible afterwards. Participants should be informed not to stop taking any medication that has been prescribed by their General Practitioner or other doctor.
Any over-the-counter medication. For details, including exceptions, see Section 6.3.	7 days or 5 half-lives (whichever is longer) before the planned study drug administration.	
Any herbal remedy or dietary supplement containing a herbal remedy.	3 weeks before the planned study drug administration.	After study completion/last visit.
Blood and plasma donation.	90 days prior to the planned study drug administration.	3 months after study completion/last visit.
Contraception: Participants must follow the contraceptive requirements as stated in Section 5.5.1.	Start times for contraceptives vary according to method used - see applicable contraceptive method in Section 5.5.1.	See specific contraception criteria in Section 5.5.1.
COVID-19 vaccination.	4 weeks before the planned first study drug administration.	After study completion / last visit.

5.5.1 Contraception requirements

Participants must abstain from unprotected sex from the dose of study drug until 120 days later.

As per the Clinical Study Facilitation Group guidance (CTFG 2020), WOCBP 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 one month prior to anticipated drug administration until 120 days 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.

Complete abstinence from sexual activity with a male partner for WOCBP is also acceptable, as long as WOCBP agree to remain abstinent for the duration of the study (from one complete menstrual cycle prior to anticipated study drug administration until Day 120 post-dose).

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

Male participants must use a condom with all partners through the study, from the time of the dose of study drug until 120 days later. Partners of male participants who are not vasectomized and who are WOCBP should use highly effective methods of birth control from one month prior to anticipated drug administration until 120 days later.

Participants who are WOCBP will be asked to inform the Investigator if they become pregnant between Day 85 and Day 120 post-dose. Male participants with a WOCBP partner will be asked to inform the Investigator if their partner becomes pregnant between Day 85 and Day 120 post-dose.

Participants who are WOCBP will be asked to perform a pregnancy test on Day 120 post-dose and report the result to the Investigator. In order to support this requirement, participants who are WOCBP will be provided with a home pregnancy testing kit at Day 85 (or at their Final Visit in cases of early withdrawal).

5.6 Criteria for withdrawal

The Investigator or designee may withdraw a participant from the study if the

participant:

- is in violation of the protocol, which may jeopardize the study results or represent a risk to the participant
- has an AE warranting withdrawal
- becomes pregnant (in line with Section 8.8)
- use of/need for a prohibited medication which in the opinion of the Sponsor or Investigator may jeopardize the study results or represent a risk to the participant
- requests to be withdrawn from the study (participant withdrawal of consent)
- is found to be considerably non-compliant with the protocol-required dosing visits
- in the Investigator's opinion, is unable to continue study participation
- is withdrawn from the study upon the request of Sponsor or the SRC, including if the Sponsor terminates the study.

5.6.1 Handling of withdrawals

If a participant withdraws or is withdrawn from the study, the Investigator will inform the Sponsor immediately. If there is a medical reason for withdrawal, the participant will remain under the supervision of the Investigator for protocol-specified safety follow up procedures.

Should any of the participants be withdrawn from the study (by the Investigator and/or Sponsor) after being dosed, all the relevant post-dose assessments should be completed as per protocol.

Should a participant withdraw themselves from the study, every effort should be made to conduct a complete Early Termination visit at an appropriate time-point. The procedures required for the 'last visit' should be performed at this visit.

A participant who fails to return for final evaluations will be contacted by the site in an attempt to have the participant comply with the protocol, in accordance with the site SOPs.

When a participant withdraws or is withdrawn from the study, the primary reason for discontinuation must be recorded in the appropriate section of the Case Report Form (CRF).

6. STUDY AND CONCOMITANT TREATMENTS

The study treatment is described below.

An '**Investigational Medicinal Product (IMP)**' is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.

6.1 Investigational Medicinal Product (IMP)

The following IMP will be used in this study:

- UPB-101

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 is presented in Table 12.

Table 12: Product descriptions

Product Description			
Product Name & Potency	**Dosing Strength**	**Dosage Form/ Fill Count**	**Administration**
UPB-101 [redacted] mg/mL	[redacted] mg	[redacted] vial solution for injection	Delivered as [redacted] mL of the formulated solution per SC injection (containing [redacted] mg UPB-101)

Bulk UPB-101 will be supplied and a Qualified Person (QP) certified by Upstream Bio or their contractor. Prior to being used on the clinical study, the IMPs will be packaged by the Upstream Bio. The prepared individual participant doses will be QP certified and dispensed by the site's pharmacy staff.

Table 13: Description of SC dosing regimens

Planned Treatment Groups	Participant Ethnicity (N Participant)	Treatment	Number of Injections to Achieve Dose	Number of Doses
1	Japanese (8)	UPB-101 [redacted] mg SC	[redacted]	Single dose
2	Japanese (8)	UPB-101 [redacted] mg SC	[redacted]	
3	Japanese (8)	UPB-101 [redacted] mg SC	[redacted]	
4	Non-Japanese Non-East Asian (8)	UPB-101 [redacted] mg SC	[redacted]	

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.

6.1.1 Packaging and labelling of IMPs

The labelling of the study drugs will be in compliance with Good Manufacturing Practice (GMP) specifications, as described in The Rules Governing Medicinal

Products in the European Union, Volume 4, Annex 13, Investigational Medicinal Products, and any other or local applicable regulations.

Sample label(s) will be submitted to the UK health authorities according to the submission requirements.

6.1.2 Drug administration

Doses of UPB-101 will be administered SC by a Research Physician and the details of dosing will be recorded in the CRF. The dosing will be verified by another member of the investigator's staff. Detailed instructions for dose administration will be included in the SOM.

6.1.3 Storage of IMPs

UPB-101 will be stored in accordance with the labelling instructions as defined in the IMPD. The IMPs will be stored securely in a temperature-controlled pharmacy with authorized access only.

The study drug will be packaged to support enrolment of the study. The study drug will be packaged according to a component schedule generated by the Sponsor. 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 drug 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 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 participant has been approved by the Investigator to be enrolled into the study. Any deviation from this must be discussed with the Sponsor's 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.

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.

6.2 Treatment allocation

6.2.1 Participant randomization

All participants of Japanese ethnicity will be assigned to a treatment regimen according to a randomization schedule generated by a statistician using PROC Plan

(treatment groups 1-3). Randomization does not occur for participants in treatment group 4 as all NJNEA participants are assigned to the same treatment ([redacted]mg UPB-101). Details regarding the unique Screening and participant number will be included in the SOM.

Eligible participants will be randomly assigned on Day 1 at the point of dosing. 8 participants will be randomized per treatment group. Thus, a total of approximately 32 male and female participants will be enrolled in the study with approximately 24 Japanese participants in treatment groups 1-3 and 8 NJNEA participants in treatment group 4.

6.2.2 Drug accountability

The designated pharmacy staff at the clinical study site will maintain accurate records of receipt and the condition of all study drugs, including dates of receipt. In addition, accurate records will be kept by the pharmacy staff of when and how much study drug is dispensed and used by each participant in the study. Any reason for departure from the protocol dispensing regimen must also be recorded.

Drug accountability records and inventory will be available for verification by the Sponsor or designee. At the completion of the study, there will be a final reconciliation of all study drugs.

Study drug must not be used for any purpose other than the present study. Remaining study drug will be returned to the Sponsor or its agent or its destruction arranged by the clinical study site according to applicable regulations and only after receipt of written authorization from the Sponsor.

6.3 Concomitant medications/permitted medications

The use of hormonal contraception and hormone replacement therapy by females is permitted.

Paracetamol may be used for pain relief, at the discretion of the PI. Ideally, paracetamol should not be used within 24 hours of dosing. After this period up to 2 g of paracetamol/day will be allowed.

The need for other medication prior to dosing may lead to participant's withdrawal from the study. If other medication is required post dosing the participant will continue in the study with all post-dose assessments to be performed as planned. In any case, the Investigator will inform the Sponsor about the concurrent medication given.

Details of all other prior and concomitant medications should be recorded by the Investigator on the CRF and source record.

6.4 COVID-19 vaccinations

Given the current COVID-19 pandemic, consideration has been made regarding participants who have had the vaccination or may be offered the vaccination during study participation (see Section 5.4).

To optimize the data collected from this study, the following rules will apply.

Participants may not be considered for participation if they:

- have received a COVID-19 vaccination within the 4 weeks prior to Day 1 of the study

- are planning on receiving a vaccination (from 4 weeks prior to Day -1 until the end of the study/last visit)

7. STUDY METHODOLOGY

7.1 Medical history

All clinically significant medical history (including any significant surgical procedures) must be recorded on the CRF for each participant. Each participant's full medical history will be obtained through direct questioning and the medical assessment at Screening and will be updated at the day of admission (Day -1). If any clinically relevant observations or investigation results are detected prior to dosing, they will be recorded as medical history.

7.2 Eligibility check

The RP will perform a study eligibility check for all study participants during Screening, as described in the Schedule of Assessments (Table 4). Further details will be provided in the SOM.

7.3 Prior and concomitant medication check

Each participant will have a prior and concomitant medication check as described in the Schedule of Assessments (Table 4).

All medications (prescription and over-the-counter), vitamin and/or mineral supplements, and herbal medicines or supplements taken at any time from the time of informed consent through to the participant's last visit will be documented on the concomitant medication CRF. Those taken within 3 months of informed consent will be recorded as 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).

7.4 Meals

Standardized meals will be provided during the study period according to the timings described in the Schedule of Assessments (Table 4).

7.5 Clinical laboratory assessments

Laboratory parameters to be measured are presented in Table 14.

Table 14: Laboratory parameters

Haematology	Biochemistry	Urinalysis
• Platelets • Haemoglobin (Hb) • Haematocrit • White blood cells • Neutrophils cell count • Eosinophils cell count • Basophils cell count • Lymphocytes cell count • Monocytes cell count • Red blood cells • Mean cell haemoglobin (MCH) • Mean corpuscular haemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • HbA1c***	• Aspartate aminotransferase (AST) • Alanine aminotransferase (ALT) • Alkaline phosphatase (ALP) • BUN*** • Gamma GT • Total bilirubin • Direct bilirubin • Creatinine • eGFR**** • Urea • Total Serum Proteins*** • Albumin • Sodium • Potassium • Calcium • Corrected calcium • Magnesium • Chloride*** • Bicarbonate*** • Amylase • Total cholesterol*** • Triglycerides*** • Serum pregnancy test* • Urine pregnancy test* • FSH* • Serum ADA and NAbs	• Leukocytes • Nitrite • Urobilinogen • Protein • pH • Blood • Specific gravity • Ketones • Bilirubin • Glucose • Urine microscopy**

Coagulation
• aPTT • PT • Fibrinogen • INR

Serology
• Hepatitis B surface Antigen (HBsAg) • Hepatitis B core Antibody (anti-HBC IgG + IgM, if IgG positive) • Hepatitis C Antibody (anti-HCV) • HIV I and II Antibodies • QuantiFERON®-TB Gold

Urine Screen for Drugs of Abuse
• Benzodiazepines • Opiates • Amphetamines • Methadone • Cocaine • Cannabinoids • Barbiturates • Cotinine

* Measured at the times presented in the Schedule of Assessments (Table 4). Serum pregnancy test for pre-menopausal women only; FSH for post-menopausal women only. ** Only if urinalysis result is abnormal (unless females menstruating in which case blood and trace protein is normal and urine microscopy will not be required). *** Measured at Screening and Day 85 only. **** calculated at Screening and Day -1 only

7.5.1 Haematology, biochemistry and coagulation

Blood samples to determine biochemistry, haematology and coagulation parameters will be taken at the times given in the Schedule of Assessments (Table 4). The date and time of collection will be recorded on the appropriate CRF pages. Further details will be described in the SOM. eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Details of this calculation will be provided in the SOM.

7.5.2 Serology

Serology testing will take place at Screening as detailed in the Schedule of Assessments (Table 4) when all participants will be tested for the parameters listed in Table 14.

The serology tests will be analyzed in the same blood sample used for biochemistry.

7.5.3 Pregnancy testing

Serum β-hCG pregnancy tests will be performed for WOCBP, as per the Schedule of Assessments (Table 4); as well as any time a pregnancy is suspected. The results of the Day -1 pregnancy test must be known before IMP administration. Participants who are pregnant will not be eligible for study participation. See Section 8.8 for follow-up instructions for women who become pregnant while in the study.

Participants who are WOCBP will agree at the time of Informed Consent to perform a pregnancy test on Day 120 post-dose and inform the Investigator of the result. In order to support this requirement, participants who are WOCBP will be provided with a home pregnancy testing kit at Day 85 (or at their Final Visit in cases of early withdrawal).

7.5.4 Urinalysis

Urine samples for determination of urinalysis parameters will be taken at the times given in the Schedule of Assessments (Table 4). As per Table 14, microscopy will be performed to confirm a clinically significant abnormal result.

7.5.5 Drugs of abuse

Urine will be tested for the drugs of abuse (DoA) as described in the Schedule of Assessments (Table 4). If a participant fails the DoA screen at Screening or Day -1, they will be excluded from the study. A repeat DoA screen can be performed where methodological reasons are believed to have led to a false positive. If a participant's results are suspected to be positive due to taking a prescribed or over-the-counter medication, e.g., flu/cold remedies, they may undergo a repeat DoA screen.

Urine will also be tested at follow-up visits in order to discourage DoA use while participants are in the study. If a positive DoA result is returned, this will be recorded in the CRF and the participant will be reminded of their responsibilities but the participant will not necessarily be withdrawn from the study.

7.5.6 FSH assessment

The postmenopausal status of women will be confirmed by:

1) a positive medical history of at least one year of amenorrhoea **and**
2) an increased blood FSH level (>30 IU/L).

FSH will be measured in postmenopausal female participants at the time of Screening (Table 4).

7.6 Alcohol breath test

An alcohol breath test will be done using an alcometer as described in the Schedule of Assessments (Table 4). If a participant tests positive to the test at Screening of Day -1 they will be excluded from the study. If a participant tests positive to the

test at a follow-up visit, this will be recorded in the CRF and the participant will be reminded of their responsibilities, but they will not be withdrawn from the study.

7.7 Vital signs (blood pressure, pulse rate, respiratory rate and tympanic temperature)

Vital signs will be measured at the time points as detailed in the Schedule of Assessments (Table 4 and Table 5). Blood pressure and pulse rate will be measured in supine position after the participant has rested comfortably for at least 5 minutes, using automated blood pressure monitors. Respiratory rate will be measured by manual counting for one minute. Temperature will be measured using tympanic thermometers.

7.8 Electrocardiographic (ECG) measurements

7.8.1 Recording of 12-lead ECGs

12-lead ECGs will be recorded at the time-points described in the Schedule of Assessments (Table 4 and Table 5) using a GE ECG recorder connected via a fixed network connection to the MUSE® Cardiology Information System (MUSE®). ECGs recorded during throughout the study will be stored electronically on the MUSE® information system. Only ECGs recorded electronically will be considered valid ECGs. ECG printouts may be filed in the participant's CRF for medical safety reviews.

Each ECG recorder will be set up to the required technical specifications and will contain the information required to identify the records. Each ECG recording will be clearly identified (with participant ID, visit date, and the actual times of ECG recordings).

12-lead ECG recordings will be made after the participants have been resting in a supine position for at least 10 minutes. The participants will avoid postural changes during the ECG recordings and clinical staff will ensure that participants are awake during the ECG recording.

At each time point, the ECG will be recorded in triplicate, to reduce variance and to improve the precision of measurement. The triplicates will be performed at approximately 1-minute intervals. Each ECG recording (tracing) will last 10 seconds. Repeat ECG will be performed until at least three 10-second ECG records per scheduled time-point meet the quality criteria set out in the SOM and the applicable SOP to enable the reading and analyzing of at least 5 complexes per derivation.

7.8.2 Safety review of 12-lead ECGs

All recorded ECGs will be reviewed by an RP and the review will be documented in the CRF. If a participant shows an abnormal ECG, additional safety recordings (including the use of 5-lead or 12-lead Holter equipment) may be made and the abnormality be followed to resolution if required.

7.8.3 Adjudication of 12-lead ECGs

ECG data will be transferred to a central ECG laboratory. ECGs from Day 22, Day 43, Day 57 and Day 71 will not be adjudicated initially, although adjudication of these ECGs may be performed later at the request of the Sponsor. ECGs from all

other timepoints will be adjudicated. Results from ECG adjudication will be transferred to RPL and be included in the study database.

7.8.4 24-hour Holter ECG

Holter recording will be performed during Screening Period days -21 to -2 as described in Table 4. Each electronic Holter ECG file will be downloaded onto the GE Gatemed Holter Analysis system. Holter data will be reported by a cardiac physiologist and reviewed by a Consultant Cardiologist. Ultimate decision for inclusion is at the discretion of the PI, in accordance with the study eligibility criteria.

7.8.5 Real time ECG telemetry

A 12-lead real-time ECG telemetry will be recorded as described in the Schedule of Assessments (Table 4 and Table 5). ECG telemetry will be monitored by the investigator or qualified member of clinical staff. The system will be managed according to local working practices. The ECG telemetry reports will be archived with study documents.

7.9 Physical examination, height, weight and BMI

The physical examination performed at Screening and at the Final Visit (Day 85) will include an assessment of the following: general appearance, skin, eyes, ears, nose, neck, lymph nodes, throat, heart, lungs, abdomen, musculoskeletal system and extremities. The timing of the physical examination is described in the Schedule of Assessments (Table 4).

A symptom-driven physical examination will be conducted at all 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 a physical exam required at the time of the Final Visit, no other physical examinations are required.

Height will be measured in centimetres and weight in kilograms. Measurements should be taken with participants wearing light clothing and without shoes, using calibrated scales for all measurements. BMI will be calculated from the height and weight. Full details will be described in the SOM.

7.10 Injection site evaluation

Injection of antibodies has been associated with injection reactions, with onset typically during or shortly after completion of the injection. For this reason, participants will be carefully observed during each injection, and at regular timepoints thereafter.

Injection site checks will be performed at the time points specified in the Schedule of Assessments (Table 4). Participants will be monitored for unusual signs and symptoms of injection site reactions such as pain, localized swelling, tenderness, or erythema. Injection site reactions will be graded as per Table 15. Injection site reactions with a severity grading of moderate or higher will be reported as an AE.

Table 15: Grading of injection site reactions

Mild	Moderate	Severe
• Symptoms may include discomfort,	• Symptoms may include pain,	• Ulceration or necrosis • Severe tissue damage

erythema, swelling and itching. • Awareness of symptoms but easily tolerated • Does not interfere with activity • Fully reversible	erythema, swelling and itching • Symptoms severe enough to disturb usual activities and/or sleep. • Treatment/intervention (including analgesia) may be indicated	• Operative intervention indicated • Symptoms incapacitating with inability to work or complete usual activities.

If a participant experiences an injection site reaction, they will continue to undergo unscheduled injection site checks until resolution. Medication to treat symptoms of an injection site reaction (including paracetamol and/or an antihistamine), may be administered per institutional standard at the discretion of the Principal Investigator.

7.11 Pharmacokinetic assessments

Blood samples will be collected at appropriate timepoints to allow serum UPB-101 concentrations and analyses including C_{max}, t_{max}, AUC_{0-t} will be assessed. If appropriate, AUC_{0-inf}, $t_{1/2}$, apparent total body clearance after dosing (CL/F), and apparent volume of distribution during the terminal elimination phase after dosing (Vz/F) will also be analyzed.

7.11.1 PK blood samples

For the timing of individual samples refer to the Schedule of Assessments (Table 4 and Table 5). The date and time of collection will be recorded on the appropriate CRF.

7.12 Pharmacodynamic assessments

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).

Blood samples will be collected at appropriate timepoints to allow asthma-related PD biomarkers to be assessed. CRP and total IgE will be assayed by the central clinical laboratory. The decision to assay the frozen samples will be based on results from earlier sample analyses of [redacted].

7.12.1 PD blood samples

For the timing of individual samples refer to the Schedule of Assessments (Table 4). The date and time of collection will be recorded on the appropriate CRF.

7.13 Immunogenicity assessments

Blood samples will be collected at appropriate timepoints to allow immunogenicity parameters (ADA, Nabs) to be assessed.

7.13.1 Immunogenicity blood samples

For the timing of individual samples refer to the Schedule of Assessments (Table 4). The date and time of collection will be recorded on the appropriate CRF.

7.14 Volume of blood sampling

The maximum total blood volume collected from participants that take part in this study will not exceed 580 mL overall. The 580 mL permitted in this study is consistent with current clinical practice in Phase 1 studies.

8. ADVERSE EVENTS

The collection, evaluation and reporting of AEs/ARs arising from this clinical study will be performed in accordance with:

- detailed guidance on the collection, verification and presentation of AE/AR reports arising from clinical trials on medicinal products for human use ('CT-3') (2011/C 172/01)
- International Conference on Harmonization (ICH) harmonised tripartite guideline on clinical safety data management: 'Definitions and standards for expedited reporting' E2A
- ICH harmonised tripartite guideline on Development Safety Update Report: E2F
- ICH guideline E2F 'Note for guidance on Development Safety Update Reports (DSUR)'.

It is the Investigator's responsibility to document and report all AEs that occur in the clinical study. The period of observation for collection of AEs extends from the signing of the ICF until the final visit. Additionally, spontaneously reported SAEs will be collected until 30 days after the final study visit. SAEs experienced after this 30-day period will only be reported if the Investigator suspects a causal relationship with the study drug.

8.1 Urgent safety measures

Regulation 30 of the Medicines for Human Use (Clinical Trials) Regulations 2004: SI 2004/1031 specifies that the Sponsor or Investigator may take appropriate urgent safety measures (USM) in order to protect the Participants of a clinical study against any immediate hazard to their health or safety.

Any USMs implemented must be reported to the Sponsor immediately. The Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC) will be notified as soon as possible and in all cases within 3 days.

8.2 Definitions

An '**Adverse Event (AE)**' is any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether considered related to it or not.

An AE may be:

- a new symptom or medical condition
- a new diagnosis
- an inter-current illness or an accident
- a worsening of a medical condition/disease(s) that existed before the start of the clinical study
- the recurrence of a disease
- an increase in frequency or intensity of episodic diseases
- a change in a laboratory or other clinical test parameter
    - the criteria to determine whether an abnormal test result should be reported as an AE/AR are as follows. The abnormal test result:
        - is associated with accompanying symptoms, and/or
        - requires additional diagnostic testing or medical/surgical intervention
- an event that leads to a change in study dosing outside of protocol-stipulated dose adjustments, or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- considered an Adverse Event by the Investigator or Sponsor.

An AE does not necessarily include the following:

- an abnormal test that needs repeating, in the absence of any of the above conditions. Any abnormal test result that is determined to be an error does not require reporting as an Adverse Event
- surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE/AR. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not AEs, if the condition leading to the measure was present before inclusion in the study and has not worsened. In the latter case, the condition should be reported as medical history.

A '**Serious Adverse Event (SAE)**' is defined as any Adverse Event that fulfils any of the following criteria:

- it results in death
- it is life-threatening (the term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- it requires a hospitalization* or prolongs existing hospitalization

- it results in persistent or significant disability/incapacity
- it is a congenital abnormality/birth defect
- it is considered medically important (medical and scientific judgement should be exercised in deciding whether other AE/ARs are to be considered serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization* but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias; convulsions that do not result in hospitalization; development of drug dependency or drug abuse).

*'Hospitalization' qualifying for an SAE does not include the following: under 24 hours; admission unrelated to an Adverse Event ,e.g., for labour and delivery, cosmetic surgery, social or administrative for temporary placement (e.g., admission due to lack of transport or support at home); admissions for diagnosis or therapy of a pre-existing condition that has not increased in severity or frequency; protocol-specified admission; pre-planned admission; admission to a rehabilitation or nursing facility; hospice; presentation to emergency departments or other urgent care centres; admissions to hospital in-patient facilities for logistical reasons only that did not result in any therapeutic intervention (e.g., awaiting consultation with and decision by senior medical staff or specialists, or for an investigation that is not immediately available); admissions to hospital in-patient facilities for investigation alone and where no significant abnormality was identified and/or no therapeutic intervention was necessary; same-day out-patient surgery.

An '**Adverse Reaction (AR)**' is a response to a medicinal product that is noxious and unintended, which occurs at any dose (in pre-approval clinical experience) or at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function (in post-approval clinical experience). The term 'reaction' means that a causal relationship between a medicinal product and an Adverse Event is at least a reasonable possibility. This means that there are facts (evidence) or arguments to suggest a causal relationship.

A '**Serious Adverse Reaction (SAR)**' is any AR that fulfils the criteria of seriousness, as defined above.

A '**Suspected Unexpected Serious Adverse Reaction (SUSAR)**' is a Serious AR that is unexpected. The 'expectedness' of a serious AR is assessed in the light of the Reference Safety Information (RSI).

8.3 Classification

8.3.1 Assessment of severity

The Investigator will assess the severity of AE/ARs using a categorical grading (mild, moderate or severe) with grading of individual AE/ARs based on global clinical assessment undertaken by an appropriately delegated Research Physician.

Changes in the severity of an AE/AR should be documented to allow an assessment of the AE/AR duration at each level of severity. AE/AR characterized as intermittent require documentation of the start and end of each incidence. Table 16 below guides categorical grading of AE/ARs.

Table 16: Categorical grading of AE/ARs

Grade	Global clinical assessment & application of grading to a diagnosis
Mild	Overall clinical condition is asymptomatic, or symptomatic with all the following characteristics: • no or minimal interference with usual social and/or functional activities • no impact, or minimal impact (e.g., of short duration or a return to normal status without intervention), upon usual self-care activities • deviation from reference range for the population and from the participant's clinically determined physiological baseline has no clinical impact and does not signal potential safety concern or unanticipated clinical risk • the condition is reversible to baseline within an anticipated timeframe • intervention or treatment is either not indicated or indicated only to increase participant's sense of wellbeing and comfort, but not due to safety concerns or risk.
Moderate	Overall clinical condition is asymptomatic or is symptomatic with no or minimal impact on usual self-care activities and one or more of the following characteristics: • greater than minimal interference with usual social and functional activities • deviation from reference range for the population and from the participant's baseline has clinical impact, but there is no acute safety concern or unanticipated risk. However, should the condition persist and/or occur more frequently, it could signal a potential safety concern or unanticipated risk and should therefore be monitored • reversibility of the condition to baseline condition takes longer than desirable or anticipated, impacting on the participant's wellbeing beyond the mere severity of the condition • further medical assessment, intervention or treatment indicated to increase participant's sense of wellbeing and comfort and to accelerate recovery and/or to prevent worsening.
Severe	Overall clinical condition is asymptomatic or is symptomatic with one or more of the following characteristics: • significant impact on usual self-care activities • inability to perform usual social and functional activities • the deviation from reference range for the population and from the participant's baseline has significant clinical impact, it is an acute safety concern or unanticipated risk and requires close and continuous monitoring • the reversibility of the condition to baseline condition takes significantly longer than desirable or anticipated, with significant impact on the participant's wellbeing • intervention or treatment essential to treat the acute manifestations and to prevent worsening • life-threatening or actually leads to death.

8.3.2 Assessment of causality

AEs will be evaluated for whether they meet the criteria for an adverse reaction (AR). An AR is a response to IMP which is noxious and unintended, and which occurs at any dose. The term "reaction" means that a causal relationship between IMP and an adverse event is at least a reasonable possibility. This

means that there are facts (evidence) or arguments to suggest a causal relationship.

- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration must be assessed.
- The Investigator will also consult the Investigator's Brochure (IB)/SmPC in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Upstream Bio. However, it is important that the Investigator attempts to make an assessment of causality before the initial transmission of the SAE data to the Sponsor or designee.
- This is due to the fact that the causality assessment is one of the criteria used when determining regulatory reporting requirements.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment of an AE to the IMP will be rated as follows by the Investigator:

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.

The Investigator should also comment on the source document whether an AE is not related to the study treatment but is related to study participation (e.g., study procedures).

The relationship to the study medication will be classified according to the categories described in Table 16.

8.3.3 Practical application of severity grading and causality assessment in relation to AR rules

Step 1: Confirm diagnosis of the AE/AR (exact term will be decided using the MedDRA), once the root cause of the clinical manifestations has been determined (rather than diagnosing individual signs, symptoms, assessments, and measurements).

Step 2: Distinguish between serious and non-serious AE/ARs using the standard definitions of what constitutes a 'serious' AE/AR (see Section 8.2).

Step 3: Assess whether there is a reasonable possibility of a relationship with the IMP.

Step 4: If there is a reasonable possibility that it is related to the IMP, apply the correct AR rules

- **'serious AR'**: The classification as 'serious' (see Sections 8.2 and 8.3) overrides the application of the categorical (mild/moderate/severe) grading system. The rules for serious AR must be applied. Categorical grading (moderate or severe) should also be independently recorded to add additional information.
- '**non-serious AR**':
    - some individual clinical manifestations, signs, symptoms, assessments, or measurements (such as QT prolongation, anaemia, thrombocytopenia, liver enzyme abnormalities) have pre-defined special AR rules, which should be applied if they occur
    - for all other non-serious ARs use the global clinical assessment and categorical grading method outlined above to assign the severity grade (Table 16). Consider:
        - the clinical significance (including presence or absence of clinical symptoms)
        - participant populations' specific references ranges and degree of deviations thereof
        - the degree of deviations from baseline
        - timing, duration, and reversibility
        - the nature and intensity of treatment required and the responses to the treatment; in addition, the potential to worsen or to become defined as serious
        - apply the general AR rules according to the assigned categorical severity grade.

8.3.4 Expectedness (Reference Safety Information)

No SARs are considered expected by the Sponsor for the purpose of expedited reporting of SUSARs.

8.4 Adverse Events of Special Interest

An Adverse Event of Special Interest (AESI) is an adverse event of scientific or medical concern specific to the Sponsor or the particular product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. It may require further investigation in order to characterize and understand them. It could be serious or non-serious and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals. If an AESI is serious, reporting procedures for SAE/SUSAR will be used. For non-serious AESI, reporting procedures will be described in the SOM.

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 graded moderate in severity or higher.

8.5 Recording of adverse events and follow-up

All (serious and non-serious) adverse events detected by the investigator or spontaneously notified by the participant at each visit/examination must be reported on the appropriate pages of the CRF. The following information should be reported for each adverse event, whether or not it can be attributed to study drug:

- Description of adverse event
- Date of onset/date of resolution
- Characteristics of the event (seriousness, intensity)
- Actions taken (treatment required, or dose adjustments must be reported in the CRF)
- Outcome
- Relationship with study drug (causality assessment) and/or study participation

A clinical laboratory abnormality will be reported as an AE if deemed to be clinically significant by the Investigator. Examples that suggest clinical significance include:

- Accompanied by clinical symptoms
- Leading to a change in treatment with IMP (e.g., dose modification, interruption, permanent discontinuation)

- Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, any other change in a concomitant medication, therapy, or treatment)
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management (e.g., discontinuation of IMP, more frequent follow-up assessments, further diagnostic investigation)

All AEs must be followed until the event is either resolved or a satisfactory explanation is found, a new baseline is met, the participant withdraws consent for participation in the study, participant is lost to follow-up, or the investigator considers it medically justifiable to terminate the follow-up. The reason(s) will be recorded in the CRF when the AE follow-up is terminated.

Whenever possible, a diagnosis should be recorded as the AE term rather than a series of symptoms/terms relating to a diagnosis. However, if the diagnosis is unknown, record sign(s) and/or symptom(s). If a diagnosis subsequently becomes available, the diagnosis should be recorded, replacing the original entry(s) where appropriate.

8.6 Reporting of Serious Adverse Events

Detailed reporting procedures will be outlined in the pharmacovigilance plan.

If an SAE occurs, the Investigators will take appropriate action immediately and will strive to identify the cause(s) of the events.

All SAEs/SUSARs will be notified by the Investigator to the Sponsor within 24 hours of awareness by email to:

[redacted]

using the 'Serious Adverse Event Form'. Emails sent to the above address will be automatically forwarded on receipt to the Upstream Bio Medical Monitor plus other individuals detailed in the Safety Management Plan.

The SAE follow-up observation period, for the concerned participants, will be jointly decided by the Investigator, Sponsor and/or SRC.

The initial report will be followed up by a full written report within 3 working days or 5 calendar days, whichever is sooner, unless no further information is available. In that case, the follow-up report will be provided as soon as new information becomes available. Further follow-up reports will be provided as and when new information becomes available. Photocopies of relevant CRF pages, such as demography, medical history, concomitant medications, as well as test results, consultant report(s), a summary of the outcome of the reaction and the Investigator's opinion of IMP relationship to the SAE/SUSAR will accompany the SAE form if and when available.

The Sponsor will also perform an evaluation of all SAEs prior to their finalization and/or reporting to any third party (e.g., REC, agency).

SUSARs will be notified to the Competent Authority and to the relevant REC(s) by Upstream Bio or its representatives within 7 days for fatal and life-threatening SUSARs or 15 days all other SUSARs.

Annual safety reporting to the national Competent Authority and the REC will be in compliance with ICH guideline E2F 'Note for guidance on Development Safety Update Reports (DSUR)'.

8.7 Potential drug-induced liver injury

Participants with DILI defined as AST or ALT ≥ 3 × ULN; total bilirubin ≥ 2 × ULN; absence of biliary obstruction/cholestasis (alkaline phosphatase < 2 × ULN) and no other explanation for the findings (e.g., viral hepatitis, chronic or acute liver disease, administration of concomitant hepatotoxic drug) must be reported as an SAE.

8.8 Pregnancy

Pregnancy is not regarded as an AE, unless there is a suspicion that the IMP may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs, and many may meet criteria for an SAE. Complications of pregnancy and abnormal outcomes of pregnancy, such as ectopic pregnancy, spontaneous abortion, intrauterine foetal demise, neonatal death, or congenital anomaly, would meet the criteria of an SAE and therefore should be reported as an SAE. Elective abortions without complications should not be handled as an AE.

If a participant becomes or is found to be pregnant while being treated or exposed to study drug, the Investigator must submit the 'Pregnancy Report Form' to the Sponsor via the same method as SAE reporting.

The participant should be followed until the outcome of the pregnancy is known (spontaneous miscarriage, elective termination, normal birth or congenital abnormality), When the outcome of the pregnancy becomes known, the Investigator must submit the 'Pregnancy Outcome Form' to the Sponsor via the same method as SAE reporting. If additional follow-up of the participant is required, the Investigator will be requested to provide the information.

Participants who are WOCBP will be instructed to report to the Sponsor any pregnancy that occurs between the final D85 Visit and D120 post-dose. Participants who are WOCBP will agree at the time of Informed Consent to perform a pregnancy test on Day 120 post-dose and inform the investigator of the result. In order to support this requirement, participants who are WOCBP will be provided with a home pregnancy testing kit at Day 85 (or at their Final Visit in cases of early withdrawal). More details regarding the Day 120 pregnancy testing process will be included in the SOM.

8.8.1 Pregnancy in female partners of male participants

If a male participant's female partner becomes or is found to be pregnant while the participant was being treated or exposed to study drug, the Investigator must submit the 'Pregnancy Report Form' to the Sponsor via the same method as SAE reporting.

Male participants may continue in the study if an accidental pregnancy of their female partner occurs despite adequate contraception.

If the male participant's partner signs informed consent, they should be followed until the outcome of the pregnancy is known (spontaneous miscarriage, elective termination, normal birth or congenital abnormality), even if the male participant

withdraws from the study. When the outcome of the pregnancy becomes known, the Investigator must submit the 'Pregnancy Outcome Form' to tranScrip via the same method as SAE reporting. If additional follow-up of the female partner is required, the Investigator will be requested to provide the information.

Male participants will be instructed to report to the Investigator any pregnancy in a WOCBP partner that occurs between the final D85 Visit and D120 post-dose.

9. QUALITY ASSURANCE AND QUALITY CONTROL

9.1 Quality assurance and quality control

Regulatory agencies may carry out a Regulatory Inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the PI and RPL agree to allow the auditor/inspector direct access to all relevant documents and to allocate their time and the time of their staff to the auditor/inspector to discuss any findings or relevant issues.

Quality Control (QC) procedures at the RPL will be implemented to ensure data recorded into the CRFs are accurate. QC checks will be carried out on an ongoing basis and according to the relevant SOPs. Records of QC checks will be documented and available for review.

Study documents routinely undergo QC to ensure their accuracy before being use and/or sent to the Sponsor. The RPL staff member providing the QC checks the documents and notes any findings/comments on the QC record form. QC checks will be carried out on an ongoing basis throughout the study and according to the relevant SOPs. Records of QC checks will be documented and available for review.

9.2 Monitoring

All aspects of the study will be carefully monitored by the Sponsor, or designee, for compliance with applicable government regulations with respect to Good Clinical Practice (GCP) and current Standard Operating Procedures.

The monitoring of this study will be performed by the Sponsor's monitor(s) or a designee in accordance with the principles of GCP as laid out in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice Guideline E6(R2) (2016).

The clinical monitor, as a representative of the Sponsor, has an obligation to follow the study closely. In doing so, the monitor will visit the Investigator and site periodically and will maintain frequent telephone and email contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff. Further details will be described in the SOM.

10. STATISTICAL ANALYSIS

10.1 Statistical analysis plan

A Statistical Analysis Plan (SAP) containing detailed statistical methodology will be written and signed off before the database hard lock. The plan may be updated to reflect adaptive features of the study as appropriate.

10.2 Statistical hypotheses

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

10.3 Sample size determination

The primary objective of the study is to characterize and compare the PK of single doses of UPB-101 in Japanese and NJNEA adults. A sample size of 8 Japanese participants enrolled in each of treatment groups 1, 2, and 3 to be administered [redacted], [redacted], and [redacted] mg of UPB-101, respectively, and 8 NJNEA participants assigned [redacted] mg of UPB-101 to treatment group 4, is considered adequate to accomplish the primary objectives of the study. The sample size is not based on formal statistical hypothesis testing. A single treatment group of NJNEA participants is included to provide a comparison to the wider dataset. Data from this study may also be compared to data from the completed SAD study conducted in healthy, NJNEA adults and the currently ongoing MAD study in adult asthmatics.

10.4 Analysis sets

The analysis of data will be based on different analysis sets according to the purpose of analysis. Participant eligibility for each analysis set will be finalized before the database hard lock. A participant who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of discontinuation.

10.4.1 Safety set

The safety set will consist of all randomized participants who received at least one injection of the IMP. The safety set will be used for the safety analyses.

10.4.2 PK set

The PK set will consist of those participants in the safety set who have sufficient blood samples taken for at least one of the PK variables to be calculated. The PK set will be used for the PK analyses.

10.4.3 PD set

The PD set will consist of those participants in the safety set for whom data are recorded for at least one timepoint where PD parameters are measured post-dose. The PD set will be used for the PD analyses.

10.4.4 Immunogenicity set

The Immunogenicity set will consist of those participants in the safety set who have blood samples taken for at least one timepoint where ADA or Nabs are measured post-dose. The Immunogenicity set will be used for the Immunogenicity analyses.

10.4.5 General considerations

Unless otherwise specified, baseline is defined as the last observed measurement, whether scheduled or unscheduled, prior to the dose of study drug.

Data for repeatedly measured assessments will be analyzed according to the nominal visit, i.e., scheduled assessment. Summaries will be presented by treatment groups with descriptive statistics (number of participants, number of observations [AEs only], mean, standard deviation, median, maximum, and minimum). Categorical variables will be tabulated by frequency and percent of participants per treatment group.

The version of MedDRA and WHODRUG that is current at the time of database soft lock will be used to code the terms for AEs, medical/surgical history and medications.

10.5 Statistical analysis of safety

All safety analyses will be conducted using the Safety Set.

Individual participant demographics (age, gender and race) and body measurement data (height, weight and BMI) at Screening will be listed. These demographic characteristics and body measurements will be summarized by each treatment group and by each population group (i.e., Japanese vs NJNEA). Other baseline characteristics will be listed only.

AE data will be listed and summarized using descriptive statistics: the number (and %) of participants who had any AEs and the number of AE episodes will be summarized by each treatment group, and by each population group (i.e., Japanese vs NJNEA). All AEs will be summarized and listed by using system organ class (SOC) and preferred term assigned to the event using Medical Dictionary for Regulatory Activities (MedDRA). Furthermore, these events will be summarized by the maximum intensity. The number of participants who had drug-related AEs will also be summarized. Any SAEs and/ or AEs that led to withdrawal will be summarized and listed.

Vital signs data (SBP, DBP, pulse rate, respiratory rate and tympanic temperature) will be listed and summarized, along with changes from baseline, using descriptive statistics (mean, median, standard deviation, minimum, maximum) by each treatment group. Out-of-reference-range values will be flagged as high (H) or low (L) and as being clinically relevant or not: the number of participants presenting out-of-range and clinically relevant values will be summarized.

All safety clinical laboratory data will be listed. Laboratory test results will also be compared to laboratory reference ranges and those values outside of the applicable range will be flagged as high (H) or low (L) and as being clinically relevant or not: the number of participants presenting out-of-range and clinically relevant values will be summarized. The quantitative laboratory data, along with changes from baseline will be summarized using descriptive statistics (mean, median, standard deviation, minimum, maximum). Change from baseline values at each assessment will be calculated as the assessment value minus the baseline value. The qualitative urinalysis data and immunogenicity will be listed only.

All unadjudicated ECG data (PR, QRS, QT, QTcB, QTcF and HR) and overall ECG evaluation will be listed. ECG data, along with changes from baseline, will be summarized using descriptive statistics (mean, median, standard deviation, minimum, maximum).

Furthermore, categorical analysis of QTcF data will be presented as follows:

- Absolute QTcF interval prolongation
  - QTcF interval > 450 ms
  - QTcF interval > 480 ms
  - QTcF interval > 500 ms
- Change from baseline in QTcF interval
  - QTcF interval increases from baseline > 30 ms
  - QTcF interval increases from baseline > 60 ms

Mean value of QTcF parameters will be plotted by dose group and time point. Out-of-reference-range values will be flagged as being clinically relevant or not. The

number of participants presenting out-of-range and clinically relevant values will be summarized.

10.6 Pharmacokinetics

10.6.1 Evaluation of pharmacokinetic parameters

Non-compartmental analysis will be used for estimation of PK parameters.

The following pharmacokinetic parameters will be calculated:

Table 17: PK parameters

Parameter	Description
C_{max}	Maximum observed serum concentration
t_{max}	Time to reach maximum observed serum concentration occurs
λz	Terminal rate constant
$t_{1/2}$	Terminal elimination half-life
$AUC_{0\text{-}inf}$	Area under the serum concentration-time curve from time zero extrapolated to infinite time
$AUC_{0\text{-}t}$	Area under the serum concentration curve from time zero up to the last quantifiable concentration
$\%AUC_{extrap}$	Percentage of AUC that is due to extrapolation from t_{last} to infinity
CL/F	Total serum clearance after dosing
V_z/F	Apparent volume of distribution estimated from the terminal phase

The individual serum concentration data, and the actual time for UBP-101 administration and blood sampling will be used in the derivation of the PK parameters. If there is any doubt as to the actual time that a sample was taken, then the scheduled time will be used.

$AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ will be calculated using the linear/log trapezoidal method, applying the linear trapezoidal rule up to C_{max} and the log trapezoidal rule for the remainder of the curve. Samples below the Lower Limit of Quantification (LLOQ) prior to the first quantifiable concentration will be set to zero. Samples with concentrations below LLOQ after the first quantifiable concentration will be set to 'missing' and omitted from the analysis. Other pharmacokinetic parameters will be calculated according to standard equations. Details will be provided in the SAP.

10.6.2 Statistical analysis on PK parameters

Serum concentrations will be listed and summarized by time point (N - the number of participants, n – the number of samples, n(LLOQ) - the number of samples <LLOQ, arithmetic mean, SD - standard deviation, CV - coefficient of variation, geometric mean, median, minimum, maximum). Descriptive statistics of concentrations will be calculated if at least one third of the individual data points are quantifiable (≥lower limit of quantification). Individual and mean with SD figures will be presented for PK concentrations by treatment group.

The PK parameters will be listed for each participant and summarized for each treatment group using descriptive statistics (N - the number of participants,

arithmetic mean, SD - standard deviation, CV - coefficient of variation, geometric mean, median, minimum, maximum).

10.7 PD analyses

All PD data will be listed and absolute values along with changes from baseline will be summarized using descriptive statistics (mean, median, standard deviation, minimum, maximum). Change from baseline values at each assessment will be calculated as the assessment value minus the baseline value.

10.8 Immunogenicity analyses

Immunogenicity (ADA and Nabs) to UPB-101 will be explored (incidence and duration) for each treatment group.

ADA data will be listed for each participant. A selected ADA-positive sample for each participant 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.

10.9 Handling of missing and incomplete data

Unrecorded values will be treated as missing. The appropriateness of the method(s) for handling missing data may be reassessed at the data review prior to database lock.

10.10 Interim analysis

No interim analyses are planned.

11. DATA MANAGEMENT

Data Management will be performed by the Data Management department of RPL. The data management process will be described in detail in the DHP.

The RPL Data Management department will be responsible for developing and maintaining the DHP; setting-up and validating the clinical study database; programming validation checks; entering data into the clinical study database; reviewing data for accuracy, completeness and consistency between the CRF and the database; and verifying adherence to the clinical pharmacology study protocol and the DHP.

Clinical data queries will be generated and resolved according to the DHP. Clinical data queries are resolved with the assistance of RPL clinical staff.

After all clinical data is entered and queries are resolved, final error rate is confirmed, and QC checks are acceptable the database will be locked.

Standard statistical analysis system (SAS®) datasets are generated from the final study database ready for analyses.

Medical coding will be performed by RPL. AEs, diagnoses from Medical History and procedures from Surgical History will be classified according to MedDRA. Concomitant medication will be coded using WHODRUG.

SAEs in the clinical database will be reconciled with the safety database.

Final raw SAS® datasets, SDTM and ADAM analyses datasets will be transferred to statistician and Sponsor.

11.1 Case report forms

A source data agreement will be signed by the Sponsor and Investigator to define what constitutes source data for all types of data captured.

CRFs will be used to record data in the study. Data should be recorded legibly onto the CRFs in black ballpoint pen. Correction fluid or covering labels must not be used.

The monitor will check data at the monitoring visits to the study site. The PI will ensure that the data in the CRFs are accurate, complete, and legible.

Data from the completed CRFs will be entered into RPL's clinical study database and validated under the direction of the Data Manager. Screening failures (participants who signed consent to take part in the study but were not randomized) as well as admission data for reserve participants (admitted as a reserve but not randomized) will not be entered into the clinical study database. Any missing, impossible (inconsistent with human life), or inconsistent recordings in the CRFs will be queried to the PI and be documented for each individual participant before clean file status is declared.

12. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

12.1 Sponsor's responsibilities

12.1.1 GCP compliance

Upstream Bio and any third party to whom aspects of the study management or monitoring have been delegated will undertake their roles for this study in compliance with all applicable regulations and ICH GCP Guidelines.

Representatives of Upstream Bio will conduct visits to Investigator sites in order to inspect study data, participants' medical records, and CRFs in accordance with current ICH Good Clinical Practice Guideline E6 (R2) (2016) and the respective local and national government regulations and guidelines. Additionally, auditors or competent authorities may review records and data.

12.1.2 Regulatory approval

Upstream Bio (or delegate) will ensure that local competent authority requirements are met before the start of the study.

12.1.3 Indemnity/liability and insurance

Upstream Bio will adhere to the recommendations of the Association of British Pharmaceutical Industry (ABPI) Guidelines. The Investigator will receive a copy of the indemnity document before study initiation. Upstream Bio will ensure that suitable insurance cover is in place prior to the start of the study. RPL will receive an insurance certificate and a statement of insurance.

12.1.4 Protocol management

Upstream Bio and/or RPL will prepare all protocols and amendments. If it becomes necessary to issue a protocol amendment during the study, Upstream Bio will

notify the Investigator and collect a documented Investigator agreement to the amendment.

12.1.5 End of study notification

RPL on behalf of Upstream Bio will submit an end of study notification to the MHRA within 90 days of the end of the study in accordance with EU Directive 2001/20/EC. The PI will be responsible for submitting these to the REC within 90 days of the end of the study.

For the purposes of this notification, the end of the study will be defined as database lock.

12.1.6 Posting or submission of summary of clinical study report to competent authorities of member states concerned and RECs

Upstream Bio or its delegate will provide result-related information on this clinical study to the MHRA, as required by the regulatory requirement and to comply with the guideline on GCP. RPL on behalf of Upstream Bio will submit a summary of the clinical study report to the concerned REC via combined review.

12.2 Investigator's responsibilities

12.2.1 GCP compliance

The Investigator must undertake to perform the study in accordance with ICH GCP Guidelines, and the applicable MHRA regulatory requirements.

It is the Investigator's responsibility to ensure that adequate time and appropriate resources are available at the study site prior to commitment to participate in this study. The Investigator should also be able to estimate or to demonstrate a potential for recruiting the required number of suitable participants within the agreed recruitment period.

The Investigator will maintain a record of appropriately qualified persons to whom the Investigator has delegated significant study-related tasks. Before the study starts, Upstream Bio (or designee) will receive an up-to-date copy of the *curriculum vitaes* for the Investigator, sub-Investigator(s), and essential study staff.

The PI will demonstrate agreement with the final clinical study by dated signature, in compliance with UK Statutory Instrument and ICH E3.

12.2.2 Protocol adherence and Investigator agreement

The PI and delegates must adhere to the CSP as detailed in this document. The PI will be responsible for including only those participants who have met CSP eligibility criteria. The PI must sign an Investigator agreement to confirm acceptance and willingness for themselves and delegates to comply with the CSP.

12.2.3 Documentation and retention of records

After completion of the study, the PI will keep all documents and data relating to the study in a secure file and/or electronically, in a secure and orderly manner. The data will be available for inspection by Upstream Bio or their representatives. Essential documents must be retained for 25 years after the final marketing approval in an ICH region or until at least 25 years have elapsed since the formal discontinuation of clinical development of UPB-101. The PI or delegate must

contact Upstream Bio before destroying any study-related documentation and it is the responsibility of Upstream Bio to inform the investigative site of when these documents can be destroyed. In addition, all participant records and other source documentation will be kept for a longer period if required by the applicable regulatory requirements.

12.3 Ethical considerations

This protocol complies with the principles of the World Medical Assembly (Helsinki 1964) and subsequent amendments.

12.3.1 Informed consent

The informed consent is a process by which a participant voluntarily confirms his/her willingness to participate in a clinical study. It is the responsibility of the PI or delegate to obtain written informed consent from participants. All consent documentation must be in accordance with applicable regulations and the ICH Good Clinical Practice Guideline E6 (R2) (2016). Each participant will be requested to sign the ICF after they have received and read the written participant information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the participant's rights and responsibilities. The pregnant partners of male participants will be requested to sign a separate ICF for pregnancy follow-up, if applicable. Signed ICFs must remain on file and must be available for verification by study monitors at any time. Another signed original of the ICF must be given to the participant or the participant's legally authorized representative. The PI or delegate will provide the Sponsor with a copy of the REC approved consent forms, and a copy of the REC written approval, prior to the start of the study.

12.3.2 Research Ethics Committee (REC) approval

It is the responsibility of the PI to submit this Clinical Study Protocol (CSP), the informed consent document (approved by Upstream Bio), relevant supporting information, and all types of participant recruitment information to the REC for review, and all must be approved prior to the start of participant screening. In addition, advertisements must be approved by the REC prior to use at the site.

Prior to implementing changes in the study, Upstream Bio and the REC must also approve any substantial amendments to the CSP and corresponding updates to informed consent documents. For non-substantial protocol amendments (that do not require REC approval) and subsequent updates of the ICF, all changes will be made in agreement with Upstream Bio and RPL.

12.4 Confidentiality

For the purposes of this Section 12.4, 'Applicable Data Protection Law' shall mean (a) the Data Protection Act 2018; (b), the UK GDPR (as defined in Section 3(10) of the Data Protection Act 2018) and (c) the General Data Protection Regulation ((EU) 2016/679) as applicable, and any applicable legislation introduced in the UK.

Data collected during this study may be used to support the development, registration, or marketing of medicinal products. Upstream Bio will control all data collected during the study and will abide by the Applicable Data Protection Law. For the purpose of the Applicable Data Protection Law, Upstream Bio will be the data controller. To the extent that RPL processes personal data on behalf of

Upstream Bio, in relation to such data RPL shall only act in accordance with the terms of this protocol, any agreements between Upstream Bio and RPL, and Upstream Bio's reasonable written instructions. RPL shall take appropriate technical and organizational measures against the unauthorized or unlawful processing of such personal data.

After participants have consented to take part in the study, Upstream Bio and/or its representatives will review their medical records and the data collected during the study. These records and data may, in addition, be reviewed by the following: independent auditors who validate the data on behalf of Upstream Bio, national or local regulatory authorities, and/or the REC which gave its approval for this study to proceed.

Although participants will be known by a unique number, their date of birth will also be collected by RPL and be used to assist Upstream Bio to verify the accuracy of the data, for example, that the results of study assessments are assigned to the correct participant. The results of this study containing the unique number, date of birth, and relevant medical information including ethnicity may be recorded and transferred to and used in other countries throughout the world. If personal data are transferred outside of the UK, RPL will ensure applicable data transfer mechanisms are in place to ensure the data receives essentially equivalent protections as are applicable in the UK. The purpose of any such transfer would be to support regulatory submissions made by Upstream Bio in such countries. The parties agree to comply with the relevant provisions of the Applicable Data Protection Law and any directions issued by the UK Information Commissioner's Office in its processing of such personal data. All nominative information in the participant's medical record will be kept strictly confidential. Nominative information shall mean the name, the address and all other personally identifiable information associated with a participant's name. Upstream Bio access to participant's data shall be performed in such a way that no participant could be identified by such data.

If there are any contradictions in terms of confidentiality requirements, the requirements of Applicable Data Protection Law will prevail.

12.5 Publication policy

If the Sponsor and RPL agree that it will be desirable to publish the results of this study, both parties will liaise in good faith to publish the results. RPL agree to obtain the Sponsor's prior written approval of such publications. Any publications should be in accordance with the agreement between Sponsor and RPL.

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