CLINICAL TRIAL PROTOCOL

Investigational Product:
UBITh® CGRP Immunotherapy (UB-313)

A Phase 1 Randomized, Double-Blind, Placebo-Controlled, First-in-Human Study to Evaluate the Safety, Tolerability, and Immunogenicity of UBITh® CGRP Immunotherapy (UB-313) in Healthy Participants

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UB-313-101	Date: 13 APRIL 2023

SYNOPSIS

Protocol Number	UB-313-101
Title of Study	A Phase 1 Randomized, Double-Blind, Placebo--Controlled, First-in-Human Study to Evaluate the Safety, Tolerability, and Immunogenicity of UBITh® CGRP Immunotherapy (UB-313) in Healthy Adults
Study Site	This study will be conducted at one study center (Center for Clinical Pharmacology) in Leuven, Belgium
Development Phase	Phase 1, First-in-human
Study Objectives	**Primary Objectives:** • To evaluate the safety and tolerability of UB-313, when administered at selected dose regimens given intramuscularly (IM) to healthy adults. • To evaluate the anti-calcitonin gene-related peptide (anti-CGRP) specific antibody responses to selected UB-313 dose regimens in healthy adults. **Secondary Objective:** • To evaluate the effects of selected UB-313 dose regimens on capsaicin-induced dermal blood flow (DBF) as a surrogate marker of target engagement. **Exploratory Objectives:** • To evaluate the effects of selected UB-313 dose regimens on CGRP concentrations in serum. • To characterize antibodies generated by UB-313. • To examine cytokine release induced by UB-313.
Endpoints	**Primary Endpoints** Safety will be assessed by adverse events (AEs), adverse events of special interest (AESIs), medically attended adverse events (MAAEs), local (injection site) and systemic (generalized) reactions (i.e., reactogenicity), clinical laboratory assessments (e.g., chemistry, hematology, urinalysis), vital signs, neurological and physical examinations, and electrocardiograms (ECGs) through the end of study. Immunogenicity will be measured by serum anti-CGRP antibody titers and analyzed from baseline to Week 16 and through the end of study (Week 44). **Secondary Outcome Measure/Endpoints** Pharmacodynamics (PD) of the immune response will be measured by the inhibition of capsaicin-induced increase in DBF and analyzed from baseline to Week 16 and either until return to baseline *or* until Week 44, whichever comes first. **Exploratory Outcome Measures/Endpoints** Exploratory outcome measures may include but are not limited to the following: • CGRP concentrations in serum through the end of study. • Antibody titers against components of UB-313 (i.e., CpG1 and UBITh1) through the end of study. • Isotype-specific anti-CGRP antibody titers through the end of study. • Cytokine release from peripheral blood mononuclear cells stimulated with a component of UB-313 (T-cell ELISpot) through Week 16.

Methodology

This single center, double-blind, placebo-controlled, multidose regimen, first-in-human (FIH) study of UB-313, an anti-CGRP peptide -based immunotherapeutic candidate, is designed to assess the safety, tolerability, and immunogenicity of 4 selected UB-313 dose regimens in healthy adults.

Screening Period

All participants will undergo Laser Speckle Contrast Imaging (LSCI) assessments at Screening to ensure a capsaicin response of at least 100% increase in DBF.

Following Screening, all eligible participants (approximately 40) will be randomized to receive 3 IM injections of UB-313 or placebo in a staggered manner by cohort as described below.

Investigational Product Dosage and Schedule:

Cohort	Number of Participants	**Dose Regimen (0.5mL)**		
		Week 1	Week 4	Week 12
1 (N=10)	8	100 µg	100 µg	100 µg
	2	Placebo	Placebo	Placebo
2 (N=10)	8	300 µg	100 µg	100 µg
	2	Placebo	Placebo	Placebo
3 (N=10)	8	300 µg	300 µg	300 µg
	2	Placebo	Placebo	Placebo
4 (N=10)	8	600 µg	100 µg	100 µg
	2	Placebo	Placebo	Placebo

Double-Blind Period

Eligible healthy participants will be enrolled into 1 of the 4 cohorts, as previously described. For safety purposes, dosing of all cohorts will be staggered. Sentinel dosing will be performed in Cohorts 1 (first dose of 100 µg), 2 (first dose of 300 µg), and 4 (first dose of 600 µg). The remaining participants in a cohort may be enrolled following a safety review conducted at least 24-hours after sentinel dosing; however, no more than 4 participants will be dosed within a 24-hour period.

Once all escalation safety evaluable participants within each of the dose levels (100 µg for Cohort 1, and 300 µg in Cohorts 2 and 3) have been observed for 1 week following their first dose of study Investigational Medicinal Product (IMP), all available safety data will be reviewed by the Safety Review Committee (SRC) before progressing to the next higher dose cohort (100 µg to 300 µg to 600 µg).

	Cohort 3 may begin dosing at least 24 hours after all participants in Cohort 2 have received their first dose, and available (blinded) safety and tolerability data have been reviewed by the SRC. Based on the available data, a decision will be made to begin dosing of Cohort 3. Participants will be provided with a diary. Starting the day of IMP administration, they will fill in the diary daily for 7 days, recording their temperature, and any solicited local and systemic symptoms of reactogenicity. **Capsaicin Challenge** A capsaicin-induced increase in DBF model will be used to assess the PDs of the UB-313-mediated immune response. Personnel who will perform these assessments will not be involved in UB-313 safety and tolerability evaluation due to the potential of unblinding. The capsaicin challenge will be conducted at Screening, Baseline before the first dose, and every 4 weeks up to Week 20 and subsequently every 8 weeks until the end of study at Week 44. After Week 16, LSCI assessment may no longer be required once the average capsaicin induced DBF increase within that cohort has returned to baseline (i.e., DBF response ±2 SD before administration of IMP within a cohort).
Total Expected Number of Participants	Approximately 40 eligible healthy male and female participants (10 per cohort) will be enrolled to receive UB-313 or placebo.
Main Inclusion Criteria	Full details of inclusion criteria are listed in the protocol. The main inclusion criteria include: • Is a male or female aged 18 to 55 years old, inclusive, at time of informed consent. • Has a body mass index between 18 and 30 kg/m^2, inclusive at Screening, and with a minimum weight of 50 kg. • Male participants and their partners of childbearing potential must commit to the use of highly effective contraceptives for the study duration and for at least 12 weeks after the last dose. Men must refrain from donating sperm during this same period. • Female participants must be of nonchildbearing potential, or, for women of childbearing potential, must be willing to practice highly effective contraception throughout the duration of the study and for at least 24 weeks following the last dose.
Main Exclusion Criteria	Full details of exclusion criteria are listed in the protocol. The main exclusion criteria include: • Has a history of clinically significant medical or psychiatric conditions, which in the opinion of the Investigator may compromise the participant's safety or the scientific value of the study, posing an unacceptable risk to the participant or interfere with the participant's ability to comply with study procedures or abide by study restrictions. • Presents any concern by the Investigator regarding safe participation in the study or for any other reason (including contraindication to MRI) that the Investigator considers the participant inappropriate for participation in the study. • Has a recent history (within the past year of Screening) of migraine headache. • Has unsuitable skin characteristics for the dermal capsaicin challenge as determined by the Investigator.

	• Has not demonstrated at least a 100% increase in DBF following capsaicin challenge as part of Screening procedures and measured through LSCI.
Investigational Medicinal Product	**UB-313** drug product is a synthetic CGRP peptide-based immunotherapy formulated in CpG1 and Adju-Phos®. It is provided in single dose vial (peptide: 100 µg, 300 µg, or 600 µg; dosage volume: 0.5 mL). **Placebo** is 0.9% sodium chloride (normal saline), preservative free for injection. IMP will be either UB-313 or placebo and can also be referred to as study drug.
Participation Duration	The total study participation will last up to 48 weeks, including: Screening period: up to 4 weeks Double-blind period: 44 weeks
Statistical Considerations	As this is an FIH study, the sample size is based on the exploratory nature of the design. No statistical power to be considered to determine the sample size. Primary time-points for immunogenicity and PD are two-fold: a) First phase at the end of Week 16 for evaluating maximal immuno-responses elicited by the 4 dosage regimens (i.e., cohorts) of UB-313 b) Second phase of response maintenance period after Week 16 until the end of study (Week 44), in which effects of the 4 dosage regimens of UB-313 on the duration of responses will be evaluated. When any cohort completes Week 16, first phase analyses can be conducted based on cleaned cohort data up to Week 16. To maintain blinding for the remainder of the study, the first phase analyses will be conducted and reviewed only by a designated and independent team before the end of study final database lock. The purpose of the early analyses of first phase data prior to the completion of the study is to have an early read out of the first part of the primary immunogenicity and PD results to refine the development plan. Design of the second phase of the study will not be changed based on results from the first phase data.

Table 1: Study Schedule of Assessments

The Investigator may perform visits outside of the scheduled study visits (unscheduled visits) listed in the Schedule of Assessments table to conduct evaluations or assessments required to protect the well-being of the participant.

Visit Number[1]	**Screen**[2]	**V1**[2,5]		**V1a**[5]	**V1b**[5]	**V2**	**V3**[5]		**V3a**[5]	**V3b**[5]	**V4**	**V5**	**V6**[5]		**V6a**[5]	**V6b**[5]	**V7**	**V8**	**V9, V10, V11**	**V12/ET**
Week	**Up to 4 wks**	**W0**				**W1**	**W4**				**W5**	**W8**	**W12**				**W13**	**W16**	**W20, W28, W36**	**W44**
Day (Visit Window)	**-28 to -1**	**D1 (-3D)**	**D1 --**	**D2**	**D3**	**D8 (±3D)**	**D29 (-3D)**	**D29 (±3D)**	**D30**	**D31**	**D36 (±3D)**	**D57 (±5D)**	**D85 (-3D)**	**D85 (±3D)**	**D86**	**D87**	**D92 (±3D)**	**D113 (±7D)**	**D141, D197, D253 (±14D)**	**D309 (±14D)**
Visit Type	**SRN**	**Pre IMP**	**IMP**	**CRU**	**TC**	**CRU**	**Pre IMP**	**IMP**	**CRU**	**TC**	**CRU**	**CRU**	**Pre IMP**	**IMP**	**CRU**	**TC**	**CRU**	**EoT CRU**	**CRU**	**EoS/ET CRU**
General Assessments and Procedures																				
Informed consent	X																			
Demographic	X																			
Medical history	X																			
Eligibility assessment	X	X																		
Medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE review[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigational Medicinal Product Administration and Assessments																				
Randomization		X																		
IMP Injection[18]			X					X						X						
Solicited local and systemic reactions assessment			X					X						X						
Extended unit stay[5]			X[5]					X						X						
Diary review[10]			X	X		X		X	X		X			X	X		X			
General Safety Assessments																				
Vital signs (pre- and post-IMP)[6,7]	X		X	X		X		X	X		X	X		X	X		X	X	X	X
Height	X																			

Visit Number[1]	**Screen**[2]	**V1**[2,5]		**V1a**[5]	**V1b**[5]	**V2**	**V3**[5]		**V3a**[5]	**V3b**[5]	**V4**	**V5**	**V6**[5]		**V6a**[5]	**V6b**[5]	**V7**	**V8**	**V9, V10, V11**	**V12/ET**
Week	**Up to 4 wks**	**W0**				**W1**	**W4**				**W5**	**W8**	**W12**				**W13**	**W16**	**W20, W28, W36**	**W44**
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Weight	X		X					X						X				X	X	X
Physical exam[4,8]	X		X					X						X				X		X
Neurological exam[4,8]	X		X					X						X				X		X
Triplicate ECGs[4]	X		X			X		X			X			X			X	X	X	X
MRI[17]	X																			
Laboratory Assessments[4,9]																				
HIV, HCV, HBV	X																			
Coagulation	X																			
Clinical chemistry[4]	X	X				X	X				X	X	X				X	X		X
Hematology[4]	X	X				X	X				X	X	X				X	X		X
Urinalysis[4]	X	X					X						X					X		X
Urine drug screen[4]	X	X					X						X							
Pre-IMP alcohol breath test[4]	X		X					X						X						
Pre-IMP pregnancy test[4,11]	X		X					X						X						
FSH[11]	X																			
Inflammatory markers[4,12]	X	X					X						X					X		X
Cytokine panel (pre- and post-IMP)[13]		X	X				X	X					X	X						
Pharmacodynamic Assessments[4]																				
Serum antibodies[4,14]		X				X	X				X	X	X				X	X	X	X
Serum CGRP[4]		X				X	X				X	X	X				X	X	X	X

Visit Number[1]	**Screen**[2]	**V1**[2,5]		**V1a**[5]	**V1b**[5]	**V2**	**V3**[5]		**V3a**[5]	**V3b**[5]	**V4**	**V5**	**V6**[5]		**V6a**[5]	**V6b**[5]	**V7**	**V8**	**V9, V10, V11**	**V12/ET**
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PBMC for ELISpot[4]		X																X		
Blood collection for research sample[4,15]		X				X	X				X	X	X				X	X	X	X
HLA typing (optional)																			X[19]	X[19]
Laser imaging and capsaicin challenge[4]	X	X					X					X	X					X	X[16]	X[16]

Abbreviations: AE = adverse event; CRU = Clinical Research Unit; D = day; DBF = dermal blood flow; ECG = electrocardiogram; EoS = End of Study; EoT = End of Treatment; ET = Early Termination; FSH = follicle-stimulating hormone; H = hour; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IM = intramuscular; IMP = investigational medicinal product; LSCI = Laser Speckle Contrast Imaging; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; SAE = serious adverse event; SD = standard deviation; SRN = Screening; TC = telephone call, V = visit

1. The Investigator may perform visits outside of the scheduled study visits (unscheduled visits) listed in the table to conduct evaluations or assessments required to protect the well-being of the participant.
2. Screening and V1 visits can be rescheduled, and Screening window may be extended.
3. AEs/SAEs recording from time of informed consent up to and including Follow-up or ET.
4. On IMP administration days, all laboratory, PD, and capsaicin assessments are to be performed prior to IMP administration.
5. After each IMP administration, (a) participants will stay for 6 hours (±2 hours) after injection for safety observation (except for sentinel participants who will stay for 24 hours after the first dose), (b) participants (except the sentinels' first dose) will have an approximately 24-hour onsite safety review including review of vital signs, temperature, diary, AEs, and medications, (c) all participants will have a telephone call approximately 48-hours post IMP injection for safety check including AE and medication review, and (d) all participants will complete a diary daily for 7 days, starting from the day of IMP administration.
6. On IMP administration days, vital signs (including temperature) will be measured before and after IMP administration.
7. Participants should be resting in a semi-recumbent position for at least 10 minutes before vital signs measurements. Semi-recumbent vital signs will include heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature.
8. Full neurological and physical examinations are to be performed during Screening, at Week 16 (EoT), Week 44 (EoS), and ET; brief (targeted) examinations may be performed at all other visits.
9. Laboratory assessments are detailed in Section 7.7 and Appendix 1.

10. A diary will be dispensed on Day 1. Participants will complete it for 7 days daily, starting on the day of each administration of IMP.
11. For females of childbearing potential only, blood pregnancy test at Screening and urine test at other visits. For females of nonchildbearing potential in post-menopausal state, FSH at screening.
12. Inflammatory measures in blood will include but are not limited to C-reactive protein and erythrocyte sedimentation rate. At Screening only, antinuclear antibody, IgM rheumatoid factor, and anti-cyclic citrullinated peptide.
13. Cytokine blood samples will be collected pre-dose and approximately 6 hours (±2 hours) post-dose, and only analyzed at the Investigator's discretion if clinically indicated; otherwise, they will be analyzed at the EoT visit. The cytokine panel will include but is not limited to IFN-γ, IL-2, IL-4, IL-6, IL-8, and TNF-α.
14. Antibody measures in blood, including but not limited to anti-CGRP target epitope, anti-UBITh, anti-CpG1, and isotyping of anti-CGRP antibodies.
15. A sample to be obtained as allowed by local regulations and participant consent.
16. After Week 16, LSCI assessment may no longer be required once the average capsaicin-induced DBF increase within that cohort has returned to baseline (i.e., DBF response ±2 SD before administration of IMP within a cohort).
17. Historic MRI within 90 days of Screening may be accepted.
18. IMP should be administered to the opposite arm that was used to take blood. Alternate arms should be used for injection visits and the arm used for IMP administration should be recorded.
19. A blood sample to be obtained for HLA typing at any post-Week 16 visit as allowed by participant consent. Blood sample is only to be collected at one visit.